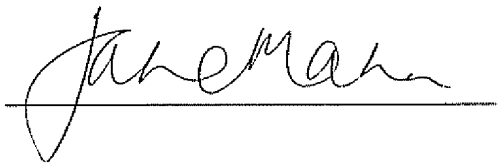
DECLARATION

I, Jane Roberta Mann, B.A., a Translator, of Frank B. Dehn & Co., 59 St Aldates, Oxford OX1 1ST, England, do declare that I have a competent knowledge of the English and German languages and that the document that is annexed hereto is a true and accurate translation of the German text of the U.S. Provisional Application Serial No. 60/251,055.

I further declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true.

I acknowledge that wilful false statements and the like are punishable by fine or imprisonment, or both [18 U.S.C. 1001] and may jeopardize the validity of the application or any patent issuing therefrom.



Signed this 12th day of July, 2006

Boehringer Ingelheim Pharma KG
D-55216 Ingelheim/Rhein
Dr Walter

Case 1/1161-KO
Priority text

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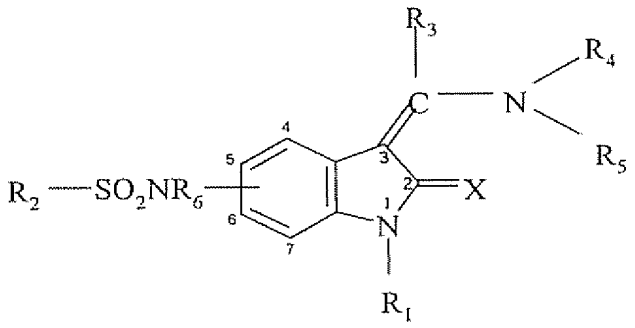
New substituted indolinones, preparation thereof and their use as pharmaceutical compositions

The present invention relates to new substituted indolinones of general formula



(I),

the isomers, the salts thereof, particularly the physiologically acceptable salts thereof which have valuable properties

The above compounds of general formula I wherein R_1 denotes a hydrogen atom or a prodrug group have valuable pharmacological properties, particularly an inhibiting effect on the proliferation of cultivated human tumour cells, but also on the proliferation of other cells, particularly endothelial cells , e g in angiogenesis, on various kinases, particularly on receptor tyrosine kinases (such as, for example, VEGFR2, EGFR, IGF1R) , non-receptor tyrosine kinases (such as e g c-src), and serine/threonine kinases (such as e g cyclin-dependent kinases), and the other compounds of the above general formula I wherein R_1 does not denote a hydrogen atom or a prodrug group, are valuable intermediate products for the preparation of the compounds mentioned above

The present invention thus relates to the above compounds of general formula I, wherein

X denotes an oxygen or sulphur atom,

R_1 denotes a hydrogen atom, a C_{1-4}-alkoxycarbonyl or C_{2-4}-alkanoyl group,

R_2 denotes a C_{1-6}-alkyl group optionally substituted by one or more halogen atoms or a phenyl group or a C_{2-6}-alkenyl group optionally substituted by a phenyl group,

wherein the phenyl moiety may be substituted in each case by a fluorine, chlorine, bromine or iodine atom, by a C_{1-3}-alkyl or C_{1-3}-alkoxy group,
a phenyl group which may be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-3}-alkyl or C_{1-3}-alkoxy groups, wherein the substituents may be identical or different,
a phenyl group substituted by a trifluoromethyl, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, cyano, aminomethyl, nitro or amino group,
a C_{4-6}-alkyl, C_{3-7}-cycloalkyl, trimethylphenyl or naphthyl group,
a 5-membered heteroaromatic group optionally substituted by a C_{1-3}-alkyl group, which contains, in the heteroaromatic moiety,
an imino group optionally substituted by a C_{1-3}-alkyl group, an oxygen or sulphur atom,
an imino group optionally substituted by a C_{1-3}-alkyl group and an oxygen, sulphur or nitrogen atom,
an imino group optionally substituted by a C_{1-3}-alkyl group and two nitrogen atoms, or
an oxygen or sulphur atom and two nitrogen atoms, and to which a phenyl ring may be fused via two adjacent carbon atoms,
or denotes a 6-membered heteroaromatic group optionally substituted by a C_{1-3}-alkyl group, which contains one or two heteroatoms in the heteroaromatic moiety and to which a phenyl ring may be fused via two adjacent carbon atoms,

R_3 denotes a hydrogen atom or a C_{1-6}-alkyl group,
a phenyl group optionally substituted by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl, hydroxy, C_{1-3}-alkoxy, C_{1-3}-alkylsulphenyl, C_{1-3}-alkylsulphinyl, C_{1-3}-alkylsulphonyl, phenylsulphenyl, phenylsulphinyl, phenylsulphonyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{2-5}-alkanoylamino or N-(C_{1-3}-alkylamino)-C_{2-5}-alkanoylamino group,

R4 denotes a phenyl or naphthyl group optionally substituted by R_7, which may additionally be substituted by a chlorine or bromine atom or a nitro group, a 5-membered heteroaromatic group which contains an imino group, an oxygen or sulphur atom or an imino group, an oxygen or sulphur atom and one or two nitrogen atoms, or

a 6-membered heteroaromatic group which contains one, two or three nitrogen atoms, while the abovementioned 5- and 6-membered heteroaromatic groups may additionally be substituted by a chlorine or bromine atom or by a methyl group or wherein a phenyl ring may be fused to the abovementioned 5- and 6-membered heteroaromatic groups via 2 adjacent carbon atoms, or

R_5 and R_6 in each case independently of one another denote hydrogen atoms or C_{1-3}-alkyl groups, and

R_7 denotes a fluorine, chlorine, bromine or iodine atom or a cyano group, a methoxy group or a C_{2-3}-alkoxy group, which may be substituted in the 2 or 3 position by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino or 5- to 7-membered cycloalkyleneimino group, while in each case an alkyl moiety in the abovementioned alkylamino and dialkylamino groups may additionally be substituted by a phenyl group,

a trifluoromethyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{2-5}-alkanoylamino, N-(C_{1-3}-alkyl)-C_{2-5}-alkanoylamino, C_{1-5}-alkylsulphonylamino, N-(C_{1-3}-alkyl)-C_{1-5}-alkylsulphonylamino, phenylsulphonylamino, N-(C_{1-3}-alkyl)-phenylsulphonylamino, aminosulphonyl, C_{1-3}-alkylaminosulphonyl or di-(C_{1-3}-alkyl)-aminosulphonyl group, while in each case an alkyl moiety in the abovementioned alkylamino and dialkylamino groups may additionally be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, 2-dimethylaminoethylaminocarbonyl or N-methyl-(2-dimethylaminoethyl)-aminocarbonyl group and in each case the alkyl moiety of the abovementioned alkanoylamino or alkysulphonylamino groups may additionally be substituted by a phenyl, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino or a 4- to 7-membered cycloalkyleneimino group,

a C_{2-4}-alkylamino group which is terminally substituted in the 2, 3- or 4 position by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, benzylamino, N-(C_{1-3}-alkyl)-benzylamino, C_{2-5}-alkanoylamino or N-(C_{1-3}-alkyl)-C_{2-5}-alkanoylamino group and wherein additionally the amino-hydrogen atom may be replaced by a C_{2-5}-alkanoyl, benzoyl, C_{1-5}-alkylsulphonyl- or phenylsulphonyl group, while the last-mentioned C_{2-5}-alkanoyl or C_{1-5}-alkylsulphonyl groups in the alkyl moiety may be substituted by a phenyl group,

a carbonyl group which is substituted by a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino, N-(C_{1-5}-alkyl)-C_{1-3}-alkylamino or C_{5-7}-cycloalkyleneimino group;

a C_{1-3}-alkyl group which may be substituted by an amino, C_{1-5}-alkylamino, C_{5-7}-cycloalkylamino or phenyl-C_{1-3}-alkylamino group which may additionally be substituted at the amino nitrogen atom in each case by a C_{1-4}-alkyl, C_{5-7}-cycloalkyl or C_{2-4}-alkenyl or C_{1-4}-alkyl group, while

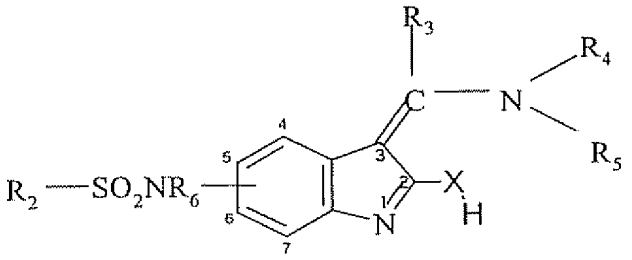
the abovementioned C_{1-4}-alkyl substituent in each case may additionally be mono-, di- or trisubstituted by a cyano, carboxy, C_{1-3}-alkoxycarbonyl, C_{2-4}-alkanoyl, pyridyl, imidazolyl, benzo[1,3]dioxol or phenyl group, while the phenyl group may be substituted by fluorine, chlorine or bromine atoms, by methyl, methoxy, trifluoromethyl, cyano or nitro groups and the substituents may be identical or different, or in the 2, 3 or 4 position by a hydroxy group,

a C_{1-3}-alkyl group which is substituted by a hydroxy, carboxy, morpholino, thiomorpholino, 1-oxo-thiomorpholino, 1,1-dioxo-thiomorpholino, piperazino, N-(C_{1-3}-alkyl)-piperazino or N-benzyl-piperazino group, by a 5- to 7-membered cycloalkenyleneimino group or by a 4- to 7-membered cycloalkyleneimino group, while the abovementioned 5- to 7-membered cycloalkyleneimino groups may be substituted by one or two C_{1-3}-alkyl groups, which may be terminally substituted by an amino or C_{2-4}-alkanoylamino group, by a C_{5-7}-cycloalkyl or phenyl group and by a hydroxy group and in the abovementioned cycloalkyleneimino groups a methylene group adjacent to the nitrogen atom may be replaced by a carbonyl group,

a C_{1-3}-alkyl group which is substituted by a 5- to 7-membered cycloalkyleneimino group, while a phenyl group optionally mono- or disubstituted by fluorine, chlorine or bromine atoms or by methyl or methoxy groups, wherein the substituents may be identical or different, or an oxazolo, imidazolo, thiazolo, pyridino, pyrazino or pyrimidino group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a methyl, methoxy or amino group is fused to the abovementioned 5- to 7-membered cycloalkyleneimino groups via 2 adjacent carbon atoms, while the abovementioned monosubstituted phenyl groups may additionally be substituted by a fluorine, chlorine or bromine atom, by a methyl, methoxy or nitro group, or

denotes an imidazolyl or 1H-C_{1-3}-alkylimidazolyl group

If R_1 denotes a hydrogen atom, the present invention also relates to the tautomeric compounds of formula I'



(I'),

The invention also relates to compounds of formula I, wherein R_1 denotes a cleavable prodrug group

The invention further relates to pharmaceutical compositions containing the pharmacologically active compound, their use and processes for preparing them

Preferred compounds of formula I are those wherein the sulphonylamino group of formula R_2-SO_2NR_6- is linked to the 5-position of the indolinone group

Also preferred are those compounds of formula I wherein
R_3 denotes a phenyl group optionally substituted by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl, hydroxy, C_{1-3}-alkoxy, C_{1-3}-alkylsulphenyl, C_{1-3}-alkylsulphinyl, C_{1-3}-alkylsulphonyl, phenylsulphenyl, phenylsulphinyl, phenylsulphonyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{2-5}-alkanoylamino or N-(C_{1-3}-alkylamino)-C_{2-5}-alkanoylamino group, more particularly a phenyl group optionally substituted by an fluorine, chlorine, bromine or iodine atom, by a C_{1-3}-alkyl, C_{1-3}-alkoxy, nitro or amino group

In another preferred embodiment R_2 denotes a C_{1-4}-alkyl group optionally substituted by one or more halogen atoms or a phenyl group, a C_{3-5}-cycloalkyl group or a C_{2-4}-alkenyl group optionally substituted by a phenyl group, wherein the phenyl moiety in each case may be substituted by a fluorine, chlorine, bromine or iodine atom or by a C_{1-3}-alkyl or C_{1-3}-alkoxy.

Moreover, the carboxy, amino or imino groups present in a compound of the above general formula I may be substituted by groups which can be cleaved *in vivo*.

In addition to the alkoxycarbonyl and alkanoyl groups already mentioned hereinbefore, groups which can be cleaved *in vivo* may also be included, such as an acyl group such as the benzoyl, pyridinoyl, pentanoyl or hexanoyl group, an allyloxycarbonyl group, a C_{1-16}-alkoxycarbonyl group such as the *tert* -butyloxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl-C_{1-6}-alkoxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a C_{1-3}-alkylsulphonyl-C_{2-4}-alkoxycarbonyl, C_{1-3}-alkoxy-C_{2-4}-alkoxy-C_{2-4}-alkoxycarbonyl or R_eCO-O-(R_dCR_e)-O-CO-group, wherein

R_e denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, phenyl- or phenyl-C_{1-3}-alkyl group,

R_e denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_d denotes a hydrogen atom or a C_{1-3}-alkyl group or a R_fCO-O-(R_gCR_h)-O-Rest wherein

R_f denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, phenyl or phenyl-C_{1-3}-alkyl group,

R_g denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_h denotes a hydrogen atom or a C_{1-3}-alkyl group,

while the abovementioned ester groups may also be used as a group which can be converted *in vivo* into a carboxy group

Preferred compounds of the above general formula I are those wherein

X denotes an oxygen atom,

R_1 denotes a hydrogen atom,

R_2 denotes a C_{1-3}-alkyl group optionally substituted by one or more fluorine atoms or a phenyl group or a C_{2-4}-alkenyl group optionally substituted by a phenyl group;

a phenyl group which may be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-3}-alkyl or C_{1-3}-alkoxy groups, wherein the substituents may be identical or different,

a phenyl group substituted by a trifluoromethyl, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, cyano, aminomethyl, nitro or amino group,
a C_{4-6}-alkyl, C_{3-7}-cycloalkyl, trimethylphenyl or naphthyl group, or
a pyridinyl, quinolyl, isoquinolyl, oxazolyl, isoxazolyl, imidazolyl or 1-(C_{1-3}-alkyl)-imidazolyl group optionally substituted by a C_{1-3}-alkyl group,

R_3 denotes a hydrogen atom or a C_{1-4}-alkyl group, or
a phenyl group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a C_{1-3}-alkyl, C_{1-3}-alkoxy, nitro or amino group,

R_4 denotes a phenyl group optionally substituted by R_7, which may additionally be substituted by a chloro or nitro group,

R_5 and R_6 in each case denote a hydrogen atom, and

R_7 denotes a fluorine, chlorine, bromine or iodine atom,
a methoxy, nitro, cyano, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylaminocarbonyl, N-(phenyl-C_{1-3}-alkyl)-C_{1-3}-alkylaminocarbonyl or 5- to 7-membered cycloalkyleneiminocarbonyl group,
a C_{1-3}-alkyl group which is substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylaminocarbonyl, N-(phenyl-C_{1-3}-alkyl)-C_{1-3}-alkylaminocarbonyl, 5- to 7-membered cycloalkyleneiminocarbonyl, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkylamino, N-(phenyl-C_{1-3}-alkyl)-C_{1-3}-alkylamino or 5- to 7-membered cycloalkyleneimino group,

while the abovementioned 5- to 7-membered cycloalkyleneimino group may be substituted by one or two C_{1-3}-alkyl groups, which may be terminally substituted by an amino or C_{2-4}-alkanoylamino group, and at the same time in the abovementioned 5- to 7-membered cycloalkyleneimino moieties a methylene group in the 2 position may be replaced by a carbonyl group or in the abovementioned 6- and 7-membered cycloalkyleneimino moieties a methylene group in the 4 position may be replaced by an oxygen atom, by an imino, N-(C_{1-3}-alkyl)-imino, N-(phenyl-C_{1-3}-alkyl)-imino or N-(C_{1-5}-alkoxycarbonyl)-imino group,

an amino, C_{1-3}-alkylamino, phenyl-C_{1-3}-alkylamino, C_{1-5}-alkanoylamino, phenyl-C_{1-4}-alkanoylamino, C_{1-5}-alkoxycarbonylamino, phenyl-C_{1-3}-alkoxycarbonylamino, C_{1-5}-alkylsulphonylamino, phenyl-C_{1-3}-alkylsulphonylamino- or phenylsulphonylamino group, wherein the hydrogen atom of the amino group may be replaced by a C_{1-3}-alkyl group, while the C_{1-3}-alkyl moiety may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylaminocarbonyl, N-(phenyl-C_{1-3}-alkyl)-C_{1-3}-alkylaminocarbonyl, 2-dimethylaminoethylaminocarbonyl, N-methyl-(2-dimethylaminoethyl)-aminocarbonyl- or C_{4-6}-cycoalkylenimnocarbonyl group or from position 2 by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkylamino, N-(phenyl-C_{1-3}-alkyl)-C_{1-3}-alkylamino, C_{2-5}-alkanoylamino, N-(C_{1-3}-alkyl)-C_{2-5}-alkanoylamino, C_{1-5}-alkoxycarbonylamino- or N-(C_{1-5}-alkoxycarbonyl)-C_{1-3}-alkylamino group,
an imidazolyl or 1-C_{1-3}-alkylimidazolyl group

Particularly preferred compounds of general formula I are those wherein

X denotes an oxygen atom,

R_1 denotes a hydrogen atom,

R_2 denotes a C_{1-3}-alkyl group optionally substituted by a phenyl group, a C_{1-3}-perfluoroalkyl group or a phenylvinyl group,
a phenyl group which may be substituted by a fluorine, chlorine, bromine or iodine atom, by a C_{1-3}-alkyl, C_{1-3}-alkoxy, nitro, amino, cyano or aminomethyl group,
a C_{4-6}-alkyl, C_{3-7}-cycloalkyl, trimethylphenyl or naphthyl group,
a pyridinyl, quinolyl, isoquinolyl, oxazolyl, isoxazolyl, imidazolyl or 1-(C_{1-3}-alkyl)-imidazolyl group optionally substituted by a C_{1-3}-alkyl group,

R_3 denotes a phenyl group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a C_{1-3}-alkyl, C_{1-3}-alkoxy, nitro or amino group,

R_4 denotes a phenyl group which may be substituted byR_7 and additionally by a chlorine atom or a nitro group, while

R_7 denotes a fluorine, chlorine, bromine or iodine atom,

a methoxy, nitro, cyano, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, benzylaminocarbonyl, N-benzyl-methylaminocarbonyl, pyrrolidinocarbonyl or piperidinocarbonyl group,
a methyl or ethyl group which may be substituted by a carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, benzylaminocarbonyl, N-benzyl-methylaminocarbonyl, pyrrolidinocarbonyl, piperidinocarbonyl, amino, C_{1-4}-alkylamino, di-C_{1-4}-alkylamino, benzylamino, N-benzyl-C_{1-4}-alkylamino, C_{2-4}-alkanoylamino, N-C_{1-4}-alkyl-C_{2-4}-alkanoylamino, tert butyloxycarbonylamino, N-methyl-tert butyloxycarbonylamino, pyrrolidino, piperidino, 4-(3-aminopropyl)-piperidino, 4-(3-acetylaminopropyl)-piperidino, dimethylpiperidino, 2-oxo-piperidino, piperazino, 4-methyl-piperazino, 4-benzyl-piperazino, 4-tert butoxycarbonyl-piperazino or morpholino group, or
an amino, methylamino, ethylamino, C_{1-3}-alkanoylamino, phenylacetylamino, tert butoxycarbonylamino, piperidinomethylcarbonylamino, C_{1-4}-alkylsulphonylamino, phenyl-methylsulphonylamino or phenylsulphonylamino group, wherein the hydrogen atom of the amino group may be replaced by a methyl, ethyl or propyl group, while the methyl or ethyl moiety in each case may be substituted by a carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, 2-dimethylaminoethylaminocarbonyl or N-methyl-(2-dimethylaminoethyl)-aminocarbonyl group or the ethyl moiety may also be substituted from position 2 by an amino, methylamino, dimethylamino, benzylalkylamino, N-benzyl-methylamino, C_{2-3}-alkanoylamino, N-methyl-C_{2-3}-alkanoylamino, tert butyloxycarbonylamino or N-methyl-tert butyloxycarbonylamino group,
an imidazolyl or 1-methylimidazolyl group,

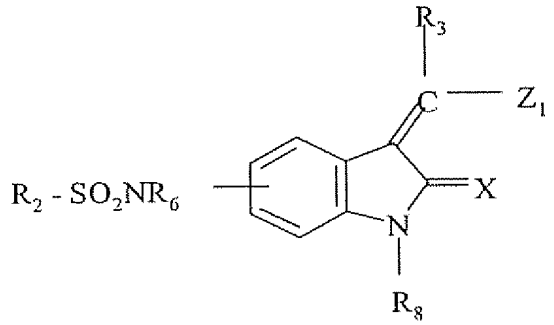
R_5 and R_6 in each case denote a hydrogen atom,

and the isomers and the salts thereof

Particularly preferred are compounds of formula I wherein R_4 denotes a phenyl group substituted by R_7 in the 3 or 4 position, particularly in the 4 position

According to the invention, the new compounds are obtained, for example, by the following methods known in principle from the literature:

a reacting a compound of general formula



(II),

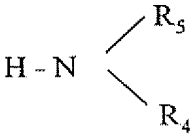
wherein

X, R_2, R_3 and R_6 are as hereinbefore defined and

R_8 has one of the meanings given for R_1 or may denote a protecting group for the nitrogen atom of the lactam group, while R_8 may also represent a bond to a solid phase optionally formed via a spacer, and

Z_1 denotes a halogen atom, a hydroxy, alkoxy or aralkoxy group, e g a chlorine or bromine atom, a methoxy, ethoxy or benzyloxy group,

with an amine of general formula



(III),

wherein

R_4 and R_5 are as hereinbefore defined,

and if necessary subsequently cleaving any protecting group used for the nitrogen atom of the lactam group or from a solid phase

The protecting group used for the nitrogen atom of the lactam group may be, for example, an acetyl, benzoyl, ethoxycarbonyl, tert butyloxycarbonyl or benzyloxycarbonyl group and the solid phase used may be a resin such as a 4-(2',4'-dimethoxyphenylaminomethyl)-phenoxy resin, while the bond may expediently be effected via the amino group, or a p-

benzyloxybenzyl alcohol resin, while the bond may expediently be effected via an intermediate member such as a 2,5-dimethoxy-4-hydroxy-benzyl derivative

The reaction is conveniently carried out in a solvent such as dimethylformamide, toluene, acetonitrile, tetrahydrofuran, dimethylsulphoxide, dichloromethane or mixtures thereof, optionally in the presence of an inert base such as triethylamine, N-ethyl-diisopropylamine or sodium hydrogen carbonate at temperatures between 20 and 175°C, while any protecting group used may simultaneously be cleaved by transamidation

If Z_1 in a compound of general formula II denotes a halogen atom, the reaction is preferably carried out in the presence of an inert base at temperatures between 20 and 120°C

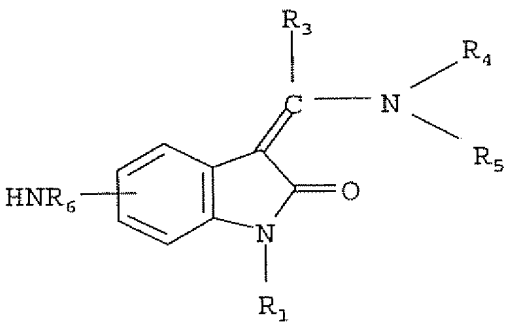
If Z_1 in a compound of general formula II denotes a hydroxy, alkoxy or aralkoxy group, the reaction is preferably carried out at temperatures between 20 and 200°C

If any protecting group used subsequently has to be cleaved, this is conveniently carried out either hydrolytically in an aqueous or alcoholic solvent, e.g. in methanol/water, ethanol/water, isopropanol/water, tetrahydrofuran/water, dioxane/water, dimethylformamide/water, methanol or ethanol in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C,

or advantageously by transamidation with an organic base such as ammonia, methylamine, butylamine, dimethylamine or piperidine in a solvent such as methanol, ethanol, dimethylformamide and mixtures thereof or in an excess of the amine used at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C

Any solid phase used is preferably cleaved using trifluoroacetic acid and water at temperatures between 0 and 35°C, preferably at ambient temperature.

b. reacting a compound of general formula



(IV),

wherein

R_1 and R_3 to R_6 are as hereinbefore defined, with a compound of general formula

$$R_2 - SO_2 - OH \quad (V),$$

wherein

R_2 is as hereinbefore defined, or with the reactive derivatives thereof

The reaction is preferably carried out in a solvent such as dichloromethane, diethylether, tetrahydrofuran, toluene, dioxane, acetonitrile, dimethylsulphoxide or dimethylformamide, optionally with a reactive derivative of a compound of general formula V such as the halide thereof, in the presence of an inorganic or tertiary organic base, preferably at temperatures between 0°C and the boiling temperature of the solvent used, preferably at temperatures between 50 and 100°C

With a corresponding sulphonic acid the reaction is preferably carried out in the presence of a dehydrating agent, e g in the presence of isobutyl chloroformate, tetraethyl orthocarbonate, trimethyl orthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benztriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylaminopyridine, N-methyl-morpholine or triethylamine, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

If according to the invention a compound of general formula I is obtained which contains an alkoxycarbonyl group, this can be converted by hydrolysis into a corresponding carboxy compound, or

if a compound of general formula I is obtained which contains an amino or alkylamino group, this may be converted by reductive alkylation into a corresponding alkylamino or dialkylamino compound, or

if a compound of general formula I is obtained which contains an amino or alkylamino group, this may be converted by acylation into a corresponding acyl compound, or

if a compound of general formula I is obtained which contains a carboxy group, this may be converted by esterification or amidation into a corresponding ester or aminocarbonyl compound, or

if a compound of general formula I is obtained which contains a nitro group, this can be converted by reduction into a corresponding amino compound, or

if a compound of general formula I is obtained which contains a cyano group, this can be converted by reduction into a corresponding aminomethyl compound

The subsequent hydrolysis is preferably carried out in an aqueous solvent, e g in water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C

The subsequent reductive alkylation is preferably carried out in a suitable solvent such as methanol, methanol/water, methanol/water/ammonia, ethanol, ether, tetrahydrofuran, dioxane or dimethylformamide, optionally with the addition of an acid such as hydrochloric acid in the presence of catalytically activated hydrogen, e g hydrogen in the presence of Raney nickel, platinum or palladium/charcoal, or in the presence of a metal hydride such as sodium

borohydride, sodium cyanoborohydride, lithium borohydride or lithium aluminium hydride at temperatures between 0 and 100°C, preferably at temperatures between 20 and 80°C

The subsequent acylation is preferably carried out in a solvent such as methylene chloride, diethylether, tetrahydrofuran, toluene, dioxane, acetonitrile, dimethylsulphoxide or dimethylformamide, optionally in the presence of an inorganic or a tertiary organic base, preferably at temperatures between 20°C and the boiling temperature of the solvent used The acylation with a corresponding acid is preferably carried out in the presence of a dehydrating agent, e g in the presence of isobutyl chloroformate, tetraethyl orthocarbonate, trimethyl orthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, thionylchloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexyl-carbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benztriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylamino-pyridine, N-methyl-morpholine or triethylamine, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C, and the acylation with a corresponding reactive compound such as an anhydride, ester, imidazolide or halide thereof is optionally carried out in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine at temperatures between 0 and 150°C, preferably at temperatures between 50 and 100°C

The subsequent esterification or amidation is expediently carried out by reacting a corresponding reactive carboxylic acid derivative with a corresponding alcohol or amine as described hereinbefore

The subsequent reduction of a nitro group is preferably carried out by hydrogenolysis, e g with hydrogen in the presence of a catalyst such as palladium/charcoal or Raney nickel in a solvent such as methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid or glacial acetic acid at temperatures of between 0 and 50°C, but

preferably at ambient temperature, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar

The subsequent reduction of a cyano group is preferably carried out by hydrogenolysis, e.g with hydrogen in the presence of a catalyst such as palladium/charcoal or Raney nickel in a solvent such as methanolic ammonia, ethanolic ammonia, ethyl acetate, dimethylformamide, dimethylformamide/acetone, dichloromethane or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid or glacial acetic acid at temperatures of between 0 and 50°C, but preferably at ambient temperature, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar

In the reactions described hereinbefore, any reactive groups present such as carboxy, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction

For example, a protecting group for a carboxyl group may be a trimethylsilyl, methyl, ethyl, tert butyl, benzyl or tetrahydropyranyl group and

protecting groups for an amino, alkylamino or imino group may be an acetyl, trifluoroacetyl, benzoyl, ethoxycarbonyl, tert butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g in water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide, at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example, hydrogenolytically, e.g with hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate, dimethylformamide,

dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid or glacial acetic acid at temperatures between 0 and 50°C, but preferably at ambient temperature, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar

A methoxybenzyl group may also be cleaved in the presence of an oxidising agent such as cerium(IV)ammonium nitrate in a solvent such as methylene chloride, acetonitrile or acetonitrile/water at temperatures of between 0 and 50°C, but preferably at ambient temperature

A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisol

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid, optionally using a solvent such as methylene chloride, dioxane, ethyl acetate or ether

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C

Moreover, chiral compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers

Thus, for example, the compounds of general formula I obtained which occur as racemates may be separated by methods known per se (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known per se, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e g esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e g on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents Optically active acids in common use are e g the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, N-acetylglutamic acid, aspartic acid, N-acetylaspartic acid or quinic acid An optically active alcohol may be for example (+)- or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)- or (-)-menthyloxycarbonyl group

Furthermore, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, maleic acid or methanesulphonic acid

Moreover, if the new compounds of formula I thus obtained contain a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine

The compounds of general formulae II to V used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature or are described in the Examples For example, the compounds of general formula IV are described in German Patent Application 198 24 922.5 of 4th June 1998

As already mentioned hereinbefore, the new compounds of general formula I wherein R_1 denotes a hydrogen atom or a prodrug group have valuable pharmacological properties, particularly an inhibiting effect on the proliferation of cultivated human cells, especially

tumour cells, but also on the proliferation of other cells, particularly endothelial cells, e g in angiogenesis

For example, the compounds listed in Table 1 were tested for their biological properties as follows:

Test 1

Inhibition of the proliferation of cultivated human tumour cells

Cells of the Leiomyosarcoma tumour cell line SK-UT-1B or non-small-cell lung tumour cell line NCI-H460 (obtained from the American Type Culture Collection (ATCC)) were cultivated in Minimum Essential Medium with non-essential amino acids (Gibco), supplemented with sodium pyruvate (1 mMol), glutamine (2 mMol) and 10% foetal calf serum (Gibco) or RPMI1640 Medium (Gibco) and 10% foetal calf serum (Gibco) and harvested in the logarithmic growth phase. Then the SK-UT-1B cells were placed in Cytostar ® multi-well plates (Amersham) at a density of 4000 cells per well or 3000 cells per well for NCI-H460 cells and incubated overnight in an incubator. Various concentrations of the compounds (dissolved in DMSO; final concentration: 0.1%) were added to the cells. After 48 hours' incubation, ^{14}C-thymidine (Amersham) was added to each well and incubation was continued for a further 24 hours. The quantity of ^{14}C-thymidine which was incorporated into the tumour cells in the presence of the inhibitor and which represents the number of cells in the S phase was measured in a Wallace 1450 Microbeta Liquid Scintillation Counter. IC_{50} values for the inhibition of the proliferation (= inhibition of incorporated ^{14}C-thymidine) were calculated, correcting for the background radiation. All the measurements were done twice.

Test 2

In vivo effects on tumour-bearing nude mice

10^6 cells [SK-UT-1B, or non-small cell lung tumour NCI-H460 (obtained from ATCC)] in a volume of 0.1 ml were injected subcutaneously into male and/or female nude mice (NMRI nu/nu; 25-35 g; N = 10-20); alternatively, small fragments of SK-UT-1B or NCI-H460 cell clumps were implanted subcutaneously. One to three weeks after injection or implantation an inhibitor was administered orally (by oesophageal tube) daily for a period of 2 to 4 weeks. The tumour size was measured three times a week using a digital sliding gauge. The effect of a compound on the tumour growth was determined as a percentage inhibition compared with a control group treated with placebo.

The following Table contains the results obtained with the *in vitro* Test 1 (++ denotes <0 01 μM, + denotes 0 01-1 0 μM):

Compound (Example No)	Inhibition of SKUT-1B proliferation
2	+
4	++
9	+
12	+
20	+
22	+
23	+
31	++
36	++
42	+
56	++
58	+
66	++
70	+
71	+
72	+
80	++
88	+
98	+
99	++
101	++
104	++
112	++
117	+
120	++

134	++
142	+
143	+
144	+
145	+
158	+
164	+
186	++
197	+

In view of their biological properties, the new compounds of general formula I, their isomers and their physiologically acceptable salts are suitable for treating conditions characterised by excessive or anomalous cell proliferation

Such diseases include (without any claim to completeness): viral infections (e g HIV and Kaposi's sarcoma); inflammation and autoimmune diseases (e g colitis, arthritis, Alzheimer's disease, glomerulonephritis and wound healing); bacterial, fungal and/or parasitic infections; leukaemias, lymphoma and solid tumours; skin diseases (e g psoriasis); bone diseases; cardiovascular diseases (e g restenosis and hypertrophy)

The new compounds may be used for the short-term or long-term treatment of the abovementioned conditions, possibly in conjunction with other state-of-the-art compounds such as other cytostatics

The dosage required to achieve the desired effect is expediently from 0 1 to 30 mg/kg, preferably 0 3 to 10 mg/kg, by intravenous route and 0 1 to 100 mg/kg, preferably 0 3 to 30 mg/kg by oral route, in each case 1 to 4 times a day For this purpose, the compounds of formula I prepared according to the invention, optionally combined with other active substances, may be formulated with one or more inert conventional carriers and/or diluents, e g with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, cetylstearylalcohol, carb-

oxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories or as solutions for injections or infusions

The Examples which follow are intended to illustrate the invention without restricting it:

Abbreviations used:

CDI	N,N'-carbonyldiimidazole
DMF	dimethylformamide
DMSO	dimethylsulphoxide
TBTU	O-(benzotriazol-1-yl)-N,N,N'-N'-bis(tetramethylene)-uronium hexafluorophosphate
THF	tetrahydrofuran

Preparation of the starting compounds:

Example I

4-[N-Acetyl-N-(2-trifluoracetylaminoethyl)-amino]-aniline

a. 4-(2-tert.Butoxycarbonylamino-ethylamino)-nitrobenzene

4.2 g (29.7 mmol) of N-tert butoxycarbonyl-ethylenediamine, 5.0 g (31.2 mmol) of 4-fluoro-nitrobenzene and 7.0 g (50.6 mmol) of potassium carbonate are stirred in 25 ml of DMSO for 9 hours at 60°C. After cooling the mixture is diluted with water and extracted with ethyl acetate. The combined organic extracts are dried and evaporated down. The residue is stirred with petroleum ether, decanted off and evaporated down again. The product is stirred with ether and suction filtered.

Yield: 3.2 g (38 % of theory),

Melting point: 119°C

R_f value: 0.5 (silica gel; toluene/ethyl acetate = 7:3)

$C_{13}H_{19}N_3O_4$ (281.31)

Mass spectrum: $(M-H)^-$ = 280

b. 4-(2-trifluoroacetylamino-ethylamino)-nitrobenzene

1.5 g (5.3 mmol) of 4-(2-tert butoxycarbonylamino-ethylamino)-nitrobenzene are stirred in 15 ml of trifluoroacetic acid for 3 hours at ambient temperature. Then 0.8 ml (5.7 mmol) of

trifluoroacetic acid anhydride are added while cooling with ice The reaction is left overnight to come up to ambient temperature It is then evaporated down, diluted with water and made alkaline with sodium hydrogen carbonate The crude product is suction filtered and purified by chromatography (silica gel; dichloromethane/methanol = 98:2)

Yield: 1 2 g (81 % of theory),

R_f value: 0 5 (silica gel; dichloromethane/methanol = 19:1)

$C_{10}H_{10}F_3N_3O_3$ (277 21)

Mass spectrum: $(M-H)^-$ = 276

c. 4-[N-Acetyl-N-(2-trifluoroacetylamino-ethyl)-amino]-nitrobenzene

0.6 g (2 1 mmol) of 4-(2-trifluoroacetylamino-ethylamino)-nitrobenzene are dissolved in 10 ml of glacial acetic acid and after the addition of 2 ml (21.2 mmol) of acetic acid anhydride stirred for 5 hours at 80°C and overnight at ambient temperature The solvent is distilled off, the residue is made alkaline with sodium hydrogen carbonate and extracted with ethyl acetate The combined organic extracts are dried and evaporated down

Yield: 0 7 g (97 % of theory),

R_f value: 0 4 (silica gel; dichloromethane/methanol = 19:1)

$C_{12}H_{12}F_3N_3O_4$ (319.24)

Mass spectrum: $(M-H)^-$ = 318

d. 4-[N-acetyl-N-(2-trifluoroacetylamino-ethyl)-amino]-aniline

0 7 g (2.1 mmol) of 4-[N-acetyl-N-(2-trifluoroacetylamino-ethyl)-amino]-nitrobenzene are dissolved in 20 ml of methanol and after the addition of 100 mg of 10% palladium on activated charcoal hydrogenated with hydrogen for 3 hours Then the catalyst is filtered off and evaporated down

Yield: 0 6 g (91 % of theory),

R_f value: 0.7 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{12}H_{14}F_3N_3O_2$ (289.26)

Mass spectrum: $(M-H)^-$ = 288, $(M+Na)^+$ = 312

The following compounds were prepared analogously to Example I :

(1) 4-[N-(2-dimethylamino-ethyl)-N-acetyl-amino]-aniline

R_f value: 0 3 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{12}H_{19}N_3O$ (221 31)

Mass spectrum: $(M+H)^+$ = 222

(2) 4-[N-(2-acetylamino-ethyl)-N-acetyl-amino]-aniline

R_f value: 0 4 (silica gel; ethyl acetate/methanol = 8:2)

$C_{12}H_{17}N_3O_2$ (235 28)

Mass spectrum: $(M+Na)^+$ = 258, $(M-H)^-$ = 234

(3) 4-[N-(2-acetylamino-ethyl)-N-propionyl-amino]-aniline

R_f value: 0 4 (silica gel; ethyl acetate/methanol = 9:1)

(4) [N-(2-propionylamino-ethyl)-N-propionyl-amino]-aniline

R_f value: 0 5 (silica gel; ethyl acetate/methanol = 9:1)

(5) 4-{N-[2-(N-acetyl-N-methyl-amino)-ethyl]-N-propionyl-amino}-aniline

R_f value: 0 5 (silica gel; dichloromethane/methanol/ammonia = 19:1:0 1)

$C_{14}H_{21}N_3O_2$ (263.34)

Mass spectrum: $(M+Na)^+$ = 286

(6) 4-{N-[2-(N-acetyl-N-methyl-amino)-ethyl]-N-acetyl-amino}-aniline

R_f value: 0 3 (silica gel; ethyl acetate/methanol = 9:1)

$C_{13}H_{19}N_3O_2$ (249 31)

Mass spectrum: $(M-H)^-$ = 248, $(M+Na)^+$ = 272

(7) 4-(dimethylaminocarbonylmethylamino)-aniline

R_f value: 0.6 (silica gel; dichloromethane/methanol/ammonia = 9:1:0.1)

$C_{10}H_{15}N_3O$ (193 25)

Mass spectrum: $(M+H)^+$ = 194, $(M+Na)^+$ = 216

(8) 4-(N-ethoxycarbonylmethyl-N-acetyl-amino)-aniline

R_f value: 0 5 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{12}H_{16}N_2O_3$ (236 27)

Mass spectrum: $(M-H)^-$ = 235, $(M+Na)^+$ = 259

(9) 4-[N-(3-dimethylamino-propyl)-N-propionyl-amino]-aniline

R_f value: 0 2 (silica gel; dichloromethane/methanol/ammonia = 8 5:1 5:0 15)

$C_{14}H_{23}N_3O$ (249 36)

Mass spectrum: $(M-H)^-$ = 248, $(M+H)^+$ = 250

Example II

4-[N-(2-benzyloxycarbonylamino-ethyl)-N-acetyl-amino)-aniline

450 mg (1 26 mmol) of 4-[N-(2-benzyloxycarbonylamino-ethyl)-N-acetyl-amino)-nitrobenzene (prepared analogously to Example I) are dissolved in 20 ml of methanol and after the addition of 100 mg of Lindlar catalyst hydrogenated for 2 hours with hydrogen The catalyst is filtered off, the solution is evaporated down

Yield: 410 mg (99 % of theory),

R_f value: 0 4 (silica gel; ethyl acetate/dichloromethane = 7:3)

$C_{18}H_{21}N_3O_3$ (327 38)

Mass spectrum: $(M+Na)^+$ = 350, $(M-H)^-$ = 326

The following compounds were prepared analogously to Example II:

(1) 4-{N-[2-(N-benzyl-N-methyl-amino)-ethyl]-N-acetyl-amino}-aniline

R_f value: 0 7 (silica gel; ethyl acetate/methanol/ammonia = 9:1:0 1)

$C_{18}H_{23}N_3O$ (297 40)

Mass spectrum: $(M+H)^+$ = 298, $(M-H)^-$ = 296

(2) 4-{N-[2-(N-benzyl-N-methyl-amino)-ethyl]-N-propionyl-amino}-aniline

R_f value: 0 5 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{19}H_{25}N_3O$ (311 43)

Mass spectrum: $(M+H)^+ = 312$

Example III

4-[N-(2-trifluoroacetylamino-ethyl)-N-methylsulphonyl-amino]-aniline

a. 4-(N-ethoxycarbonylmethyl-N-methylsulphonyl-amino)-nitrobenzene

20 g (92 5 mmol) of 4-(methylsulphonylamino)-nitroaniline are dissolved in 155 ml of DMSO and while cooling with ice 11.7 (104 mmol) of potassium tert butoxide are added After 1 hour 13 5 ml (121 mmol) of ethyl bromoacetate are added The mixture is stirred for 18 hours at ambient temperature and the reaction solution is then poured onto ice water It is extracted with ethyl acetate The organic phase is washed with water, dried and freed from the solvent *in vacuo* The residue is triturated with petroleum ether

Yield: 27 1 g (97 % of theory),

Melting point: 73-75°C

R_f value: 0 8 (silica gel; dichloromethane/ethyl acetate = 9:1)

$C_{11}H_{14}N_2O_6S$ (302 31)

Mass spectrum: $(M+Na)^+ = 325$, $(M-H)^- = 301$

b. 4-(N-carboxymethyl-N-methylsulphonyl-amino)-nitrobenzene

26 8 g (88 6 mmol) of 4-(N-ethoxycarbonylmethyl-N-methylsulphonyl-amino)-nitrobenzene are suspended in 320 ml of ethanol and combined with 268 ml of 1 N sodium hydroxide solution The mixture is stirred for one hour at ambient temperature and then 268 ml of 1 N hydrochloric acid are added The precipitate formed is suction filtered, washed with a little ethanol and ether, and dried *in vacuo*

Yield: 21 9 g (90% of theory),

Melting point: 215-218°C

R_f value: 0 6 (silica gel; dichloromethane/methanol/glacial acetic acid = 9:1:0 1)

$C_9H_{10}N_2O_6S$ (274 25)

Mass spectrum: $(M-H)^- = 273$

c. 4-(N-aminocarbonylmethyl-N-methylsulphonyl-amino)-nitrobenzene

2 5 g (15 4 mmol) of CDI are added to a solution of 3 g (10 9 mmol) of 4-(N-carboxymethyl-N-methylsulphonyl-amino)-nitrobenzene in 30 ml of DMF The mixture is stirred for one hour at ambient temperature Then NH_3 is piped in at 0°C over a period of 10 min After 2 hours' stirring at ambient temperature 100 ml of water are added The mixture is extracted with ethyl acetate, the organic phase is washed with water, dried over magnesium sulphate and evaporated to dryness The residue is stirred with water, suction filtered and washed with ether

Yield: 2 3 g (78% of theory),

Melting point: 160°C

R_f value: 0 5 (silica gel; ethyl acetate/dichloromethane = 3:2)

d. 4-[N-(2-aminoethyl)-N-methylsulphonyl-amino]-nitrobenzene

2 3 g (8 4 mmol) of 4-(N-aminocarbonylmethyl-N-methylsulphonyl-amino)-nitrobenzene are refluxed in 35 ml (35 mmol) of borane-THF (1 M solution in THF) 7 hours Then 30 ml of 6 N hydrochloric acid are added, and the mixture is refluxed for another 8 hours The solvent is distilled off, the residue is mixed with water and extracted with ethyl acetate The aqueous phase is made alkaline with potassium carbonate and extracted with dichloromethane The organic phase is separated off, dried and evaporated down

Yield: 1 7 g (77 % of theory),

R_f value: 0 5 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_9H_{13}N_3O_4S$ (259 29)

Mass spectrum: $(M+H)^+ = 260$, $(M-H)^- = 258$

e. 4-[N-(2-trifluoroacetylamino-ethyl)-N-methylsulphonyl-amino]-aniline

Prepared analogously to Example Ib by reacting 4-[N-(2-aminoethyl)-N-methylsulphonyl-amino]-nitrobenzene with trifluoroacetic acid anhydride in trifluoroacetic acid followed by catalytic reduction analogously to Example Id with 10% palladium/charcoal in methanol

Yield: 76 % of theory,

R_f value: 0 6 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

The following compounds were prepared analogously to Example III:

(1) 4-(N-ethoxycarbonylmethyl-N-ethylsulphonyl-amino)-aniline

R_f value: 0 5 (silica gel; petroleum ether/ethyl acetate = 4:6)

Melting point: 78°C

$C_{12}H_{18}N_2O_4S$ (286 35)

Mass spectrum: $(M+Na)^+ = 309$, $(2M+Na)^+ = 593$

(2) 4-{N-[2-(N-acetyl-N-methyl-amino)-ethyl]-N-methylsulphonyl-amino)-aniline

R_f value: 0 5 (silica gel; dichloromethane/methanol/ammonia = 19:1:0 1)

(3) 4-[N-(2-acetylamino-ethyl)-N-methylsulphonyl-amino]-aniline

R_f value: 0 5 (silica gel; dichloromethane/methanol/ammonia = 19:1:0 1)

$C_{11}H_{17}N_3O_3S$ (271 34)

Mass spectrum: $(M+H)^+ = 272$, $(M+Na)^+ = 294$

(4) 4-{N-[2-(N-acetyl-N-methyl-amino)-ethyl]-N-ethylsulphonyl-amino}-aniline

R_f value: 0 5 (silica gel; dichloromethane/methanol/ammonia = 19:1:0 1)

Melting point: 140°C

$C_{13}H_{21}N_3O_3S$ (299 39)

Mass spectrum: $M^+ = 299$

(5) 4-[N-(2-acetylamino-ethyl)-N-ethylsulphonyl-amino)-aniline

R_f value: 0 4 (silica gel; dichloromethane/methanol/ammonia = 19:1:0 1)

$C_{12}H_{19}N_3O_3S$ (285 36)

Mass spectrum: $(M-H)^- = 284$, $(M+Na)^+ = 308$

(6) 4-{N-[2-(N-methyl-N-trifluoroacetyl-amino)-ethyl]-N-methylsulphonyl-amino}-aniline

R_f value: 0 5 (silica gel; dichloromethane/ethyl acetate = 9:1)

Example IV

4-[N-(2-dimethylamino-ethyl)-N-phenylsulphonyl-amino]-aniline

a. N-(2-dimethylamino-ethyl)-phenylsulphonamide

2 8 g (30 mmol) of N,N-dimethylethylenediamine are placed in 100 ml of dichloromethane and 8 3 ml (60 mmol) of triethylamine While cooling with ice a solution of 3 9 ml (30 mmol) of benzenesulphonic acid chloride in 100 ml of dichloromethane is added dropwise and the mixture is stirred overnight at ambient temperature Water is added and the mixture is extracted with dichloromethane The organic phase is dried and evaporated down

Yield: 6 8 g (99 % of theory),

R_f value: 0 4 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{10}H_{16}N_2O_2S$ (228 23)

Mass spectrum: $(M-H)^- = 227$, $(M+H)^+ = 229$

b. 4-[N-(2-dimethylamino-ethyl)-N-phenylsulphonyl-amino]-nitrobenzene

6 8 g (29 8 mmol) of N-(2-dimethylamino-ethyl)-phenylsulphonamide are dissolved in 100 ml of DMF and combined with 1 3 g (30 mmol) of sodium hydride (55% in oil) The mixture is stirred for one hour at ambient temperature Then 4 2 g (29 8 mmol) of 4-fluoro-nitrobenzene are added, and stirring is continued for another 16 hours After the addition of 300 ml of water the mixture is extracted with ethyl acetate The organic phase is washed with water, dried and evaporated down The residue is acidified with 1 N hydrochloric acid and washed with ethyl acetate The aqueous phase is then made basic again with sodium hydroxide solution and extracted with ethyl acetate The organic phase is dried and evaporated down

Yield: 6 0 g (58 % of theory),

R_f value: 0 4 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{16}H_{19}N_3O_4S$ (349 41)

Mass spectrum: $(M-H)^- = 348$, $(M+H)^+ = 350$

c. 4-[N-(2-dimethylaminoethyl)-N-phenylsulphonyl-amino]-aniline

Prepared analogously to Example Id by catalytic hydrogenation of 6 g (17 2 mmol) of 4-[N-(2-dimethylamino-ethyl)-N-phenylsulphonyl-amino]-nitrobenzene

Yield: 5 5 g (99 % of theory),

R_f value: 0 5 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{16}H_{21}N_3O_2S$ (319 43)

Mass spectrum: $(M+H)^+ = 320$

The following compounds were prepared analogously to Example IV:

(1) 4-[N-(2-dimethylamino-ethyl)-N-propylsulphonyl-amino]-aniline

R_f value: 0 4 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{13}H_{23}N_3O_2S$ (285 41)

Mass spectrum: $(M+H)^+ = 286$, $(M-H)^- = 284$

(2) 4-[N-(2-dimethylamino-ethyl)-N-butylsulphonyl-amino]-aniline

R_f value: 0 4 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{14}H_{25}N_3O_2S$ (299 43)

Mass spectrum: $(M+H)^+ = 300$

(3) 4-[N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino]-aniline

Melting point: 112-113°C

R_f value: 0 4 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{12}H_{21}N_3O_2S$ (271 38)

Mass spectrum: $(M+H)^+ = 272$, $(M+Na)^+ = 294$

(4) 4-[N-(2-dimethylamino-ethyl)-N-benzylsulphonyl-amino]-aniline

R_f value: 0 3 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{17}H_{23}N_3O_2S$ (333 46)

Mass spectrum: $(M+H)^+ = 334$, $(M+Na)^+ = 356$

(5) 3-chloro-4-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-aniline

Melting point: 145-148°C

R_f value: 0 5 (silica gel; dichloromethane/ethanol/ammonia = 5:1:0 01)

$C_{11}H_{18}ClN_3O_2S$ (291 80)

Mass spectrum: $(M+H)^+$ = 294, 292, $(M-H)^-$ = 292, 290

(6) 3-amino-4-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-aniline

R_f value: 0.3 (silica gel; dichloromethane/methanol/ammonia = 9:1:0.1)

$C_{11}H_{20}N_4O_2S$ (272.37)

Mass spectrum: $(M+H)^+$ = 273

(7) 4-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-aniline

R_f value: 0.3 (silica gel; dichloromethane/methanol/ammonia = 9:1:0.1)

Melting point: 147-148°C

$C_{11}H_{19}N_3O_2S$ (257.36)

Mass spectrum: $(M+H)^+$ = 258, $(M+Na)^+$ = 280

Example V

3-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-aniline

a. 3-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-nitrobenzene

5 g (23.1 mmol) of 3-methylsulphonylamino-nitrobenzene are dissolved in 50 ml of DMSO and combined with 6.5 g (58 mmol) of potassium tert. butoxide while cooling with ice. The solution thus obtained is added dropwise to a solution of 5 g (34.7 mmol) of 2-chloro-N,N-dimethyl-ethylamine in 30 ml of DMSO. The mixture is stirred for 2 hours at ambient temperature and then heated for 6 hours to 100 °C. After cooling to ambient temperature 400 ml of water are added. The mixture is extracted with ethyl acetate. Water and 1 N hydrochloric acid are added to the combined organic phases until an acid reaction is obtained. The aqueous phase is washed with ethyl acetate. Then the aqueous phase is made alkaline with sodium carbonate and the product is extracted with ethyl acetate. Drying the combined organic phases over magnesium sulphate and eliminating the solvents *in vacuo* yields the product as a red oil.

Yield: 2.07 g (31 % of theory),

R_f value: 0.3 (silica gel; ethyl acetate/methanol = 4:1)

$C_{11}H_{17}N_3O_4S$ (287.34)

Mass spectrum: $(M-H)^-$ = 286, $(M+H)^+$ = 288

b. 3-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-aniline

Prepared analogously to Example 1d by catalytic hydrogenation of 1 9 g (6 8 mmol) of 3-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-nitrobenzene over palladium/charcoal

Yield: 1 8 g (99% of theory),

R_f value: 0.3 (silica gel; ethyl acetate/methanol/NH_4OH = 8:2:0 1)

$C_{11}H_{19}N_3O_2S$ (257 36)

Mass spectrum: $(M-H)^-$ = 256, $(M+H)^+$ = 258

Example VI

4-(4-benzyl-piperazinomethyl)-aniline

a. 4-(4-tert.butoxycarbonyl-piperazinomethyl)-nitrobenzene

A mixture of 10 6 g (57 mmol) of N-tert butoxycarbonyl-piperazine, 10 8 g (62 7 mmol) of 4-nitrobenzylchloride, 23 8 ml (171 mmol) of triethylamine in 100 ml of dichloromethane is stirred for 12 hours at 70°C. After diluting with water the organic phase is separated off, dried and evaporated down.

Yield: 19 g (99 % of theory),

Melting point: 83-84°C

R_f value: 0 7 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{16}H_{23}N_3O_4$ (321 38)

Mass spectrum: $(M+H)^+$ = 322, $(M-H)^-$ = 320

b. 4-piperazinomethyl-nitrobenzene-dihydrochloride

6 4 g (20 mmol) of 4-(4-tert butoxycarbonyl-piperazinomethyl)-nitrobenzene are dissolved in 20 ml of dichloromethane and combined with 40 ml of ethyl acetate/HCl The reaction solution is diluted with ether, the precipitate formed is suction filtered as a crude product and then reacted further.

Yield: 5 4 g (92 % of theory),

Melting point: 257-258°C

R_f value: 0 3 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

c. 4-(4-benzylpiperazinomethyl)-nitrobenzene

The free base is produced from 1 5 g (5 mmol) of 4-piperazinomethyl-nitrobenzene-dihydrochloride by dissolving in 25 ml of 1 N sodium hydroxide solution, extracting with ethyl acetate and then eliminating the solvent *in vacuo* The solid thus obtained is combined with 2 5 ml of 2 N acetic acid, 0 5 ml (5 5 mmol) of benzaldehyde and 50 ml of methanol and, after the addition of 0 7 g (5 mmol) of sodium cyanoborohydride, stirred for2 hours Then the pH is adjusted to acid with 1 N hydrochloric acid and the reaction solution is washed with ether The aqueous phase is then made basic with sodium hydroxide solution The product is extracted with ether, the combined ether extracts are dried and the solvent is eliminated *in vacuo*

Yield: 1 3 g (84 % of theory),

R_f value: 0 6 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{18}H_{21}N_3O_2$ (311 39)

Mass spectrum: $(M+H)^+ = 312$

d. 4-(4-benzylpiperazinomethyl)-aniline

Prepared analogously to Example Id by catalytic hydrogenation of 1 3 g (4 2 mmol) of 4-(4-benzylpiperazinomethyl)-nitrobenzene over palladium/charcoal

Yield: 1 2 g (87 % of theory),

Melting point: 88-89°C

$C_{18}H_{23}N_3$ (281 4)

Mass spectrum: $(M+H)^+ = 282$

Example VII

4-(4-tert.butoxycarbonyl-piperazinomethyl)-aniline

a. 4-(4-tert.butoxycarbonyl-piperazinomethyl)-nitrobenzene

10 6 g (57 mmol) of N-tert butoxycarbonyl-piperazine are dissolved in 100 ml of dichloromethane and combined with 10 7 g (63 mmol) of 4-nitrobenzylchloride and 24 ml

(171 mmol) of triethylamine The mixture is refluxed for 12 hours After cooling to ambient temperature the reaction solution is washed several times with water The organic phase is dried over magnesium sulphate and then evaporated to dryness

Yield: 17 g (99%) of theory

Melting point: 83-84°C

R_f value: 0 7 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{16}H_{23}N_3O_4$ (321 38)

Mass spectrum: $(M+H)^+ = 322$, $(M-H)^- = 320$

b. 4-(4-tert.butoxycarbonyl-piperazinomethyl)-aniline

Prepared analogously to Example Id by catalytic hydrogenation of 4-(4-tert butoxycarbonyl-piperazinomethyl)-nitrobenzene with Raney nickel in ethyl acetate/methanol (1:1)

Melting point: 106-107°C

R_f value: 0 6 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{16}H_{25}N_3O_2$ (291 39)

Mass spectrum: $(M+H)^+ = 292$, $(M+Na)^+ = 314$

The following compounds were prepared analogously to Example VII:

(1) 4-(pyrrolidin-1-yl-methyl)-aniline

R_f value: 0 2 (silica gel; dichloromethane/methanol/NH_4OH = 5:1:0 01)

Melting point: 48-50°C

(2) 4-(4-methylpiperazinomethyl)-aniline

Melting point: 94-95°C

R_f value: 0 2 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

$C_{12}H_{19}N_3$ (205 31)

Mass spectrum: $(M+H)^+ = 206$

(3) 3-(dimethylaminomethyl)-aniline

R_f value: 0 7 (silica gel; ethyl acetate)

Melting point: 43-46°C

(4) 4-(dimethylaminomethyl)-aniline

R_f value: 0.13 (silica gel; ethyl acetate/ethanol = 8:2)

(5) 4-(2-dimethylamino-ethyl)-aniline

R_f value: 0.3 (silica gel; dichloromethane/methanol/ammonia = 19:1:0.1)

Melting point: 40°C

$C_{10}H_{16}N_2$ (164.25)

Mass spectrum: $(M+H)^+ = 165$

(6) 4-(N-benzyl-N-methyl-aminomethyl)-aniline

R_f value: 0.5 (silica gel; dichloromethane/methanol/ammonia = 10:1:0.01)

Melting point: 48-50°C

$C_{15}H_{18}N_2$ (226.32)

Mass spectrum: $(M+H)^+ = 227$

(7) 4-piperidinomethyl-aniline

R_f value: 0.2 (silica gel; dichloromethane/methanol/ammonia = 9:1:0.1)

Melting point: 88-89°C

(8) 4-(2,6-dimethylpiperidino-methyl)-aniline

R_f value: 0.3 (silica gel; dichloromethane/methanol/ammonia = 5:1:0.01)

Melting point: 112-115°C

(9) 4-(N-ethyl-N-methyl-aminomethyl)-aniline

R_f value: 0.4 (silica gel; dichloromethane/methanol/ammonia = 10:1:0.1)

$C_{10}H_{16}N_2$ (164.25)

Mass spectrum: $(M+H)^+ = 165$

(10) 4-[4-(3-trifluoromethylcarbonylamino-propyl)-piperidinomethyl]-aniline

R_f value: 0.4 (silica gel; dichloromethane/methanol/ammonia = 10:1:0.1)

$C_{17}H_{24}F_3N_3O$ (343.40)

Mass spectrum: $(M+H)^+ = 344$

(11) 4-(N-tert butoxycarbonyl-N-propyl-aminomethyl)-aniline

$C_{15}H_{24}N_2O_2$ (264 37)

Mass spectrum: $(M+Na)^+ = 287$

(12) 4-(N-tert butoxycarbonyl-N-butyl-aminomethyl)-aniline

R_f value: 0 19 (silica gel; dichloromethane/methanol = 50:1)

$C_{16}H_{26}N_2O_2$ (278 40)

Mass spectrum: $(M+Na)^+ = 301$

(13) 4-(N-tert butoxycarbonyl-N-ethyl-aminomethyl)-aniline

Melting point: 85°C

R_f value: 0 3 (silica gel; dichloromethane/methanol/ = 50:1)

$C_{14}H_{22}N_2O_2$ (250 34)

Mass spectrum: $(M+Na)^+ = 273$

Example VIII

4-(2-oxopiperidinomethyl)-aniline

6 4 g (42 mmol) of 4-nitrobenzaldehyde are dissolved in 150 ml of methanol and combined with 4 9 g (42 mmol) of 5-aminovaleric acid and 1 8 g (29 mmol) of sodium cyanoborohydride The mixture is stirred for 18 hours at ambient temperature and then carefully mixed with 20 ml of conc hydrochloric acid The solvent is eliminated *in vacuo*, the residue is taken up in water and extracted with dichloromethane The residue obtained after evaporation is chromatographed on silica gel (dichloromethane/methanol, 4:1) A mixture of methyl 5-(4-nitrobenzylamino)-pentanoate and 4-(2-oxopiperidinomethyl)-nitrobenzene is obtained which is dissolved in 100 methanol and combined with 50 ml of 1 N sodium hydroxide solution The mixture is stirred for one hour at ambient temperature, 50 ml of 1 N hydrochloric acid are added and the reaction solution is evaporated down to 100 ml The

aqueous phase thus obtained is extracted with dichloromethane The combined organic phases are dried over sodium sulphate and evaporated to dryness

The residue is hydrogenated analogously to Example Id over Raney nickel in methanol under a hydrogen atmosphere of 3 bar for 11 hours

Total yield: 2 2 g (26 % of theory),

R_f value: 0 63 (silica gel; dichloromethane/methanol = 9:1)

Example XIV

4-(N-piperidinomethylcarbonyl-N-methyl-amino)-aniline

a. 4-(N-bromomethylcarbonyl-N-methyl-amino)-nitrobenzene

23 5 g (0 15 mol) of N-methyl-4-nitroaniline are dissolved in 400 ml of dioxane and combined with 22 2 g (0 3 mol) of lithium carbonate Then 32 2 g (0 18 mol) of bromoacetylbromide are added dropwise in such a way that the internal temperature does not exceed 33°C After 18 hours' stirring the reaction solution is evaporated down to 100 ml, combined with 500 ml of water and stirred for 1 hour The precipitate formed is suction filtered, washed with water and dried The crude product is stirred in 400 ml of ethyl acetate at 40°C Then the insoluble matter is filtered off, the solution is evaporated down and the solid residue is triturated with ether

Yield: 35 g (83 % of theory),

Melting point: 85-87°C

b. 4-(N-piperidinomethylcarbonyl-N-methyl-amino)-nitrobenzene

5 4 g (20 mmol) of 4-(N-bromomethylcarbonyl-N-methyl-amino)-nitrobenzene are dissolved in 100 ml of acetone and combined with 5 5 g (40 mmol) of potassium carbonate 3 ml (30 mmol) of piperidine are slowly added dropwise and the mixture is stirred for 18 hours at ambient temperature The reaction solution is filtered, and the filtrate is evaporated to dryness The residue is dissolved in ethyl acetate, washed with water, dried over magnesium sulphate and evaporated to dryness

Yield: 5.6 g (99 % of theory)

c. 4-(N-piperidinomethylcarbonyl-N-methyl-amino)-aniline

Prepared analogously to Example Id by catalytic hydrogenation of 4-(N-piperidinomethylcarbonyl-N-methyl-amino)-nitrobenzene in methanol over palladium/charcoal

Yield 4 95 g (99% of theory)

Example X

4-(tert.butoxycarbonylaminomethyl)-aniline

20 g (164 mmol) of 4-aminobenzylamine and 20 2 g (210 mmol) of triethylamine are dissolved in 100 ml of dioxane and 50 ml of water 35 8 g (165 mmol) of di-tert butyl-dicarbonate dissolved in 60 ml of dioxane are added to this solution while cooling with ice and the resulting mixture is stirred for 18 hours at ambient temperature Then the solvent is distilled off *in vacuo*, the residue is distributed in ethyl acetate/water The combined organic extracts are freed from solvent *in vacuo* The crude product is heated in 200 ml of petroleum ether, cooled slowly with vigorous stirring and the crystalline product is removed by suction filtering

Yield: 34 8 g (96 % of theory),

Melting point: 77-78°C

Example XI

4-(1H-imidazol-2-yl)-aniline

7 2 g (50 mmol) of 2-phenylimidazol are dissolved in 100 ml of conc sulphuric acid While cooling with ice 5 0 g (62 mmol) of ammonium nitrate are added in batches and the mixture is stirred for 2 5 hours The reaction solution is then poured onto ice, made basic with conc. ammonia and the crystalline product is suction filtered The nitro compound thus obtained is catalytically hydrogenated analogously to Example Id in DMF over palladium/charcoal

Yield: 24 % of theory,

R_f value: 0 4 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

Example XII

Pyridine-2-sulphonic acid chloride

5 0 g (45 mmol) of pyridine-2-thiol are dissolved in 40 ml of conc hydrochloric acid While the solution is cooled with ice, chlorine gas is piped in over a period of 2 5 hours In order to destroy any excess gas a washing bottle containing 1 N sodium thiosulphate solution is attached Then the reaction solution is poured onto ice water and extracted with ether and dichloromethane. The organic phases are combined, dried and freed from solvent *in vacuo* The crude product is further reacted immediately

Yield: 8 g (100 % of theory)

Example XIII

Pyridine-3-sulphonic acid chloride hydrochloride

1 g (6 3 mmol) of pyridine-3-sulphonic acid and 1 4 g (6 7 mmol) of phosphorus pentachloride are stirred for 2 hours at 150°C After cooling, excess phosphorus pentachloride is eliminated *in vacuo*. The crude product is further reacted immediately

Yield: 1 2 g (91 % of theory)

Preparation of the end products:

Example 1

(Z)-3-{1-[4-(N-acetyl-N-(2-aminoethyl)-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone

a. 1-acetyl-2-indolinone

13.3 g (0.1 mol) of 2-indolinone and 30 ml of acetic anhydride are stirred for 3 hours at 170°C. After cooling the mixture is combined with 150 ml of ice water, the crystalline product is suction filtered, washed with water and dried.

Yield: 16.6 g (95 % of theory),

Melting point: 129-130°C.

b. 1-acetyl-5-nitro-2-indolinone

0.5 g (2.8 mmol) of 1-acetyl-2-indolinone are placed in 4 ml of conc. sulphuric acid. At a temperature of -10 to -5°C, 0.3 g (3.4 mmol) of ammonium nitrate are added in batches. After 45 minutes the mixture is poured onto ammonia/ice water, the crystalline precipitate is suction filtered, washed with water and dried. The crude product is recrystallised from 70 ml of cyclohexane.

Yield: 0.2 g (32 % of theory),

Melting point: 150-157°C.

R_f value: 0.7 (silica gel; cyclohexane/ethyl acetate = 4:6)

c. 1-acetyl-5-amino-2-indolinone

30.0 g (136 mmol) of 1-acetyl-5-nitro-2-indolinone are dissolved in a mixture of 650 ml of dichloromethane and 650 ml of methanol and after the addition of 5 g of 10% palladium on activated charcoal the mixture is hydrogenated for 45 minutes with hydrogen. Then the catalyst is filtered off and evaporated down.

Yield: 22.4 g (87 % of theory),

Melting point: 177°C

R_f value: 0.7 (silica gel; ethyl acetate)

$C_{10}H_{10}N_2O_2$ (190 20)

Mass spectrum: $(M-H)^-$ = 189, $(M+Na)^+$ = 213

d. 1-acetyl-5-phenylsulphonylamino-2-indolinone

20 0 g (105 mmol) of 1-acetyl-5-amino-2-indolinone are placed in 200 ml of pyridine, combined with 15 3 ml (120 mmol) of benzenesulphonic acid chloride while cooling with ice and stirred for 2 hours Then the mixture is poured onto 1 8 l of water and suction filtered The crude product is stirred into acetone, suction filtered and dried

Yield: 30.5 g (88 % of theory),

Melting point: 245°C

R_f value: 0 5 (silica gel; dichloromethane/ethyl acetate = 9:1)

$C_{16}H_{14}N_2O_4S$ (330.37)

Mass spectrum: $(M-H)^-$ = 329, $(M+Na)^+$ = 353

e. 1-acetyl-3-(1-ethoxy-1-phenyl-methylidene)-5-(N-acetyl-N-phenylsulphonyl-amino)-2-indolinone

8 0 g (24 2 mmol) of 1-acetyl-5-phenylsulphonylamino-2-indolinone are dissolved in 150 ml of acetic anhydride and after the addition of 20 ml (88 1 mmol) of triethyl orthobenzoate refluxed for 6 hours The solvent is distilled off, the residue is triturated with ether, suction filtered and dried.

Yield: 7 8 g (64 % of theory),

Melting point: 237°C

R_f value: 0.7 (silica gel; dichloromethane/ethyl acetate = 19:1)

$C_{27}H_{24}N_2O_6S$ (504.57)

Mass spectrum: M^+ = 504

f. (Z)-3-{1-[4-(N-acetyl-N-(2-aminoethyl)-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone

A mixture of 0 5 g (1 mmol) of 1-acetyl-3-(1-ethoxy-1-phenyl-methylidene)-5-(N-acetyl-N-phenylsulphonyl-amino)-2-indolinone and 0 3 g (1 2 mmol) of 4-[N-acetyl-N-(2-trifluoroacetylamino-ethyl)-amino]-aniline are stirred in 5 ml of DMF for 6 hours at 120°C. After cooling to ambient temperature 5 ml of methanol and 3 ml (6 mmol) of 2 N sodium

hydroxide solution are added, and the mixture is stirred for 30 minutes. The reaction mixture is diluted with 50 ml of water and the crystalline precipitate is suction filtered and dried. The residue is chromatographed on silica gel (dichloromethane/methanol/ammonia = 9:1:0.1)

Yield: 0.3 g (49 % of theory),

Melting point: 216°C

R_f value: 0.3 (silica gel; dichloromethane/methanol/ammonia = 9:1:0.1)

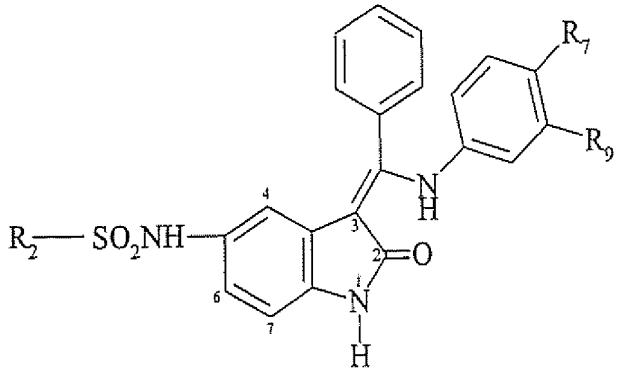
$C_{31}H_{29}N_5O_4S$ (567.67)

Mass spectrum: $(M-H)^-$ = 566, $(M+H)^+$ = 568

Examples 2 to 97

Using the intermediate products prepared in Examples I to XIII, the compounds of formula IA of Examples 2 to 97 listed in Table I are prepared analogously to Example 1

Table I



(IA),

Example	R_2	R_7	R_9	chemical name	Melting point (°C)
2	phenyl	N-(2-aminoethyl)-N-methylsulphonyl-amino	H	(Z)-3-{1-[4-(N-(2-aminoethyl)-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	245
3	phenyl	N-(2-methylamino-ethyl)-N-methylsulphonyl-amino	H	(Z)-3-{1-[4-(N-(2-methylamino-ethyl)-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	227-229
4	phenyl	N-(2-dimethylamino-ethyl)-N-phenylsulphonyl-amino	H	(Z)-3-{1-[4-(N-(2-dimethylaminoethyl)-N-phenylsulphonyl-amino)-phenylamino)-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	168-169

5	phenyl	N-(2-dimethylamino-ethyl)-N-propylsulphonyl-amino	H	(Z)-3-{1-[4-(N-(2-dimethylamino-ethyl)-N-propylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	137-138
6	phenyl	N-(2-dimethylamino-ethyl)-N-butylsulphonyl-amino	H	(Z)-3-{1-[4-(N-(2-dimethylamino-ethyl)-N-butylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	197-198
7	phenyl	4-benzyl-piperazino-methyl	H	(Z)-3-{1-[4-(4-benzyl-piperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	130 (decomp.)
8	phenyl	N-acetyl-N-(2-benzyl-oxycarbonylamino-ethyl)-amino	H	(Z)-3-{1-[4-(N-acetyl-N-(2-benzyloxycarbonylamino-ethyl)-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonyl-amino-2-indolinone	180
9	phenyl	4-methylpiperazino-methyl	H	(Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	243-244
10	phenyl	morpholinomethyl	H	(Z)-3-{1-[4-(morpholinomethyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	243-244
11	phenyl	2-oxopiperidinomethyl	H	(Z)-3-{1-[4-(2-oxopiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-	311-312

				indolinone	
12	phenyl	pyrrolidin-1-ylmethyl	H	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	228-229
13	phenyl	4-tert.butoxycarbonyl-piperazinomethyl	H	(Z)-3-{1-[4-(4-tert.butoxycarbonyl-piperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	160-161
14	phenyl	N-methyl-N-formyl-amino	H	(Z)-3-{1-[4-(N-methyl-N-formyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	315-317
15	phenyl	tert.butoxycarbonyl-amino	H	(Z)-3-[1-(4-tert.butoxycarbonylamino-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	96-98
16	phenyl	N-methyl-N-propionyl-amino	H	(Z)-3-{1-[4-(N-methyl-N-propionyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	208-210
17	phenyl	acetylamino	H	(Z)-3-[1-(4-acetylamino-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	245-247
18	phenyl	N-methyl-N-ethylsulphonyl-amino	H	(Z)-3-{1-[4-(N-methyl-N-ethylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-	278-280

				phenylsulphonylamino-2-indolinone	
19	phenyl	propionylamino	H	(Z)-3-[1-(4-propionylamino-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	254-256
20	phenyl	N-methyl-N-acetyl-amino	H	(Z)-3-{1-[4-(N-methyl-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	283-285
21	phenyl	N-acetyl-N-[2-(N-benzyl-N-methyl-amino)-ethyl]-amino	H	(Z)-3-{1-[4-(N-acetyl-N-(2-(N-benzyl-N-methyl-amino)-ethyl)-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	237
22	phenyl	H	H	(Z)-3-(1-phenylamino-1-phenyl-methylidene)-5-phenylsulphonylamino-2-indolinone	283
23	phenyl	chloro	H	(Z)-3-[1-(4-chlorophenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	295
24	phenyl	N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino	H	(Z)-3-{1-[4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	234
25	phenyl	N-(2-dimethylamino-ethyl)-N-acetyl-amino	H	(Z)-3-{1-[4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	202

26	phenyl	N-piperidinomethyl-carbonyl-N-methyl-amino	H	(Z)-3-{1-[4-(N-piperidinomethylcarbonyl-N-methyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	269
27	phenyl	H	N-(2-dimethylamino-ethyl)-N-methyl-sulphonyl-amino	(Z)-3-{1-[3-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	140
28	phenyl	H	dimethylamino-methyl	(Z)-3-[1-(3-dimethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	140
29	phenyl	N-(2-acetylamino-ethyl)-N-acetyl-amino	H	(Z)-3-{1-[4-(N-(2-acetylamino-ethyl)-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	229
30	phenyl	N-(2-acetylamino-ethyl)-N-propionyl-amino	H	(Z)-3-{1-[4-(N-(2-acetylamino-ethyl)-N-propionyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	278
31	phenyl	N-(2-propionylamino-ethyl)-N-propionyl-amino	H	(Z)-3-{1-[4-(N-(2-propionylamino-ethyl)-N-propionyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	280
32	phenyl	N-[2-(N-acetyl-N-	H	(Z)-3-{1-[4-(N-(2-(N-acetyl-N-methyl-amino)-ethyl)-N-	180 (decomp.)

		methyl-amino)-ethyl]-N-methylsulphonyl-amino		methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	
33	phenyl	N-(2-acetylamino-ethyl)-N-methylsulphonyl-amino]	H	(Z)-3-{1-[4-(N-(2-acetylamino-ethyl)-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	171
34	phenyl	4-{N-[2-(N-acetyl-N-methyl-amino)-ethyl]-N-ethylsulphonyl-amino	H	(Z)-3-{1-[4-(N-(2-(N-acetyl-N-methyl-amino)-ethyl)-N-ethylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	216
35	phenyl	cyano	H	(Z)-3-[1-(4-cyanophenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	291-293
36	phenyl	dimethylaminomethyl	H	(Z)-3-[1-(4-dimethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indole	255-256
37	phenyl	2-dimethylamino-ethyl	H	(Z)-3-[1-(4-(2-dimethylamino-ethyl)-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	302-303
38	phenyl	N-(2-acetylamino-ethyl)-N-	H	(Z)-3-{1-[4-(N-(2-acetylamino-ethyl)-N-ethylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-	158

		ethylsulphonyl-amino		phenylsulphonylamino-2-indolinone	
39	phenyl	acetylaminomethyl	H	(Z)-3-[1-(4-acetylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	289-290
40	phenyl	N-[2-(N-acetyl-N-methyl-amino)-ethyl]-N-acetyl-amino	H	(Z)-3-{1-[4-(N-(2-(N-acetyl-N-methyl-amino)-ethyl)-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	297
41	phenyl	methylsulphonylamino	H	(Z)-3-[1-(4-methylsulphonylamino-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	258-260
42	phenyl	N-methyl-N-methylsulphonyl-amino	H	(Z)-3-[1-(4-(N-methyl-N-methylsulphonyl-amino)-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	306-308
43	phenyl	ethylsulphonylamino	H	(Z)-3-[1-(4-ethylsulphonylamino-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	177-179
44	phenyl	N-[2-(N-acetyl-N-methyl-amino)-ethyl]-N-propionyl-amino	H	(Z)-3-{1-[4-(N-(2-(N-acetyl-N-methyl-amino)-ethyl)-N-propionyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	250
45	phenyl	N-[2-(N-benzyl-N-methyl-amino)-ethyl]-	H	(Z)-3-{1-[4-(N-(2-(N-benzyl-N-methyl-amino)-ethyl)-N-propionyl-amino)-phenylamino]-1-phenyl-methylidene}-	220

		N-propionyl-amino		5-phenylsulphonylamino-2-indolinone	
46	phenyl	dimethylamino-carbonylmethylamino	H	(Z)-3-{1-[4-(dimethylaminocarbonylmethylamino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	230-231
47	phenyl	formylamino	H	(Z)-3-[1-(4-formylamino-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	305-307
48	phenyl	(2,6-dimethylpiperi-dino)-methyl	H	(Z)-3-{1-[4-((2,6-dimethylpiperidino)-methyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	144-145
49	phenyl	N-(dimethyl-aminomethylcarbonyl)-N-methyl-amino	H	(Z)-3-{1-[4-(N-dimethylaminomethylcarbonyl-N-methyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	242
50	phenyl	N-(2-dimethylamino-ethyl)-N-benzylsulphonyl-amino	H	(Z)-3-{1-[4-(N-(2-dimethylamino-ethyl)-N-benzylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	80 (decomp.)
51	phenyl	2-propionylamino-ethylamino	H	(Z)-3-{1-[4-(2-propionylamino-ethylamino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	216
52	phenyl	N-tert.butoxycarbonyl-N-propyl-aminomethyl	H	(Z)-3-{1-[4-(N-tert.butoxycarbonyl-N-propyl-aminomethyl)-phenylamino]-1-phenyl-methylidene}-5-	215

				phenylsulphonylamino-2-indolinone	
53	phenyl	N-tert.butoxycarbonyl-N-butyl-aminomethyl	H	(Z)-3-{1-[4-(N-tert.butoxycarbonyl-N-butyl-aminomethyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	207
54	phenyl	methyl	H	(Z)-3-[1-(4-methylphenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	192
55	phenyl	N-methyl-N-ethyl-aminomethyl	H	(Z)-3-[1-(4-(N-methyl-N-ethyl-aminomethyl)-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	256
56	phenyl	N-methyl-N-piperidi-nomethylcarbonyl-amino	H	(Z)-3-[1-(4-(N-methyl-N-piperidinomethylcarbonyl-amino)-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	274-276
57	benzyl	dimethylaminomethyl	H	(Z)-3-{1-[4-dimethylaminomethyl-phenylamino]-1-phenyl-methylidene}-5-benzylsulphonylamino-2-indolinone	242-243
58	benzyl	pyrrolidin-1-ylmethyl	H	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-benzylsulphonylamino-2-indolinone	228
59	benzyl	tert.butoxycarbonyl-aminomethyl	H	(Z)-3-[1-(4-tert.butoxycarbonylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-	205

				benzylsulphonylamino-2-indolinone	
60	benzyl	(2,6-dimethylpiperidi-no)-methyl	H	(Z)-3-{1-[4-((2,6-dimethylpiperidino)-methyl)-phenylamino]-1-phenyl-methylidene}-5-benzylsulphonylamino-2-indolinone	140 (decomp.)
61	3-methoxy-phenyl	(2,6-dimethylpiperidi-no)-methyl	H	(Z)-3-{1-[4-((2,6-dimethylpiperidino)-methyl)-phenylamino]-1-phenyl-methylidene}-5-(3-methoxyphenylsulphonylamino)-2-indolinone	186
62	3-methoxy-phenyl	pyrrolidin-1-ylmethyl	H	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-methoxyphenylsulphonylamino)-2-indolinone	233
63	3-methoxy-phenyl	tert.butoxycarbonyl-aminomethyl	H	(Z)-3-[1-(4-tert.butoxycarbonylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-(3-methoxyphenylsulphonylamino)-2-indolinone	189
64	3-nitro-phenyl	pyrrolidin-1-ylmethyl	H	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino)-1-phenyl-methylidene}-5-(3-nitrophenylsulphonylamino)-2-indolinone	181
65	3-nitro-phenyl	tert.butoxycarbonyl-aminomethyl	H	(Z)-3-[1-(4-tert.butoxycarbonylaminomethyl)-phenylamino)-1-phenyl-methylidene]-5-(3-nitrophenylsulphonylamino)-2-indolinone	238°C (decomp.)
66	3-nitro-	(2,6-dimethylpiperidi-	H	(Z)-3-{1-[4-((2,6-dimethylpiperidino)-methyl)-	215

	phenyl	no)-methyl		phenylamino]-1-phenyl-methylidene}-5-(3-nitrophenylsulphonylamino)-2-indolinone	
67	2-cyano-phenyl	4-methylpiperazino-methyl	H	(Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(2-cyanophenylsulphonylamino)-2-indolinone	255 (decomp.)
68	3-amino-carbonyl-phenyl	4-methylpiperazino-methyl	H	(Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-aminocarbonyl-phenyl sulphonylamino)-2-indolinone	278 (decomp.)
69	ethyl	H	H	(Z)-3-(1-phenylamino-1-phenyl-methylidene)-5-ethylsulphonylamino-2-indolinone	309
70	ethyl	dimethylaminomethyl	H	(Z)-3-{1-[4-dimethylaminomethyl-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone	230
71	ethyl	N-benzyl-N-methyl-aminomethyl	H	(Z)-3-{1-[4-(N-benzyl-N-methyl-aminomethyl)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone	223
72	ethyl	2-dimethylamino-ethyl	H	(Z)-3-{1-[4-(2-dimethylamino-ethyl)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone	242
73	ethyl	N-(2-dimethylamino-	H	(Z)-3-{1-[4-(N-(2-dimethylamino-ethyl)-N-	240

		ethyl)-N-methyl-sulphonyl-amino		methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone	
74	ethyl	Cl	H	(Z)-3-[1-(4-chlorophenylamino)-1-phenyl-methylidene]-5-ethylsulphonylamino-2-indolinone	274
75	ethyl	nitro	H	(Z)-3-{1-[4-nitrophenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone	270
76	phenyl	N-tert.butoxycarbonyl-N-ethyl-aminomethyl	H	(Z)-3-{1-[4-(N-tert.butoxycarbonyl-N-ethyl-aminomethyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	225
77	ethyl	4-(3-aminopropyl)-piperidinomethyl	H	(Z)-3-{1-[4-(4-(3-aminopropyl)-piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone	224
78	ethyl	4-(3-acetylamino-propyl)-piperidinomethyl	H	(Z)-3-{1-[4-(4-(3-acetylamino-propyl)-piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone	145
79	pyridin-3-yl	dimethylaminomethyl	H	(Z)-3-{1-[4-dimethylaminomethyl-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-indolinone	246-247
80	pyridin-3-yl	pyrrolidin-1-ylmethyl	H	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-	235-236

				indolinone	
81	pyridin-3-yl	N-acetyl-N-methyl-amino	H	(Z)-3-{1-[4-(N-acetyl-N-methyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-indolinone	240-241
82	pyridin-3-yl	N-methyl-N-methylsulphonyl-amino	H	(Z)-3-{1-[4-(N-methyl-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-indolinone	286-287
83	pyridin-3-yl	N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino	H	(Z)-3-{1-[4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-indolinone	249-250
84	pyridin-3-yl	1H-imidazol-2-yl	H	(Z)-3-{1-[4-(1H-imidazol-2-yl)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-indolinone	222-223
85	pyridin-3-yl	1-methyl-1H-imidazol-2-yl	H	(Z)-3-{1-[4-(1-methyl-1H-imidazol-2-yl)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-indolinone	230-231
86	pyridin-3-yl	dimethylamino-carbonyl	H	(Z)-3-{1-[4-dimethylaminocarbonyl-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-indolinone	171-172

87	pyridin-3-yl	4-methyl-piperazinomethyl	H	(Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-indolinone	258-259
88	pyridin-3-yl	pyrrolidin-1-ylcarbonyl	H	(Z)-3-{1-[4-(pyrrolidin-1-ylcarbonyl)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-indolinone	284-285
89	pyridin-3-yl	N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino	Cl	(Z)-3-{1-[3-chloro-4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-indolinone	261-262
90	pyridin-3-yl	N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino	NH_2	(Z)-3-{1-[3-amino-4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-indolinone	272-273
91	pyridin-2-yl	4-methyl-piperazinomethyl	H	(Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-2-ylsulphonylamino)-2-indolinone	210 (decomp.)
92	pyridin-2-yl	N-acetyl-N-[2-(N-benzyl-N-methyl-amino)-ethyl]-amino	H	(Z)-3-{1-[4-(N-acetyl-N-(2-(N-benzyl-N-methyl-amino)-ethyl)-amino)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-2-ylsulphonylamino)-2-indolinone	232-235

93	pyridin-2-yl	N-(3-dimethylamino-propyl)-N-propionyl-amino	H	(Z)-3-{1-[4-(N-(3-dimethylamino-propyl)-N-propionyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-2-ylsulphonylamino)-2-indolinone	217-219
94	pyridin-2-yl	N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino	H	(Z)-3-{1-[4-(N-(3-dimethylamino-propyl)-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-2-ylsulphonylamino)-2-indolinone	258-260
95	pyridin-2-yl	N-(3-dimethylamino-propyl)-N-propylsulphonyl-amino	H	(Z)-3-{1-[4-(N-(3-dimethylamino-propyl)-N-propylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-2-ylsulphonylamino)-2-indolinone	256-257
96	pyridin-2-yl	N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]	H	(Z)-3-{1-[4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-2-ylsulphonylamino)-2-indolinone	269-271
97	pyridin-2-yl	N-piperidinomethyl-carbonyl-N-methyl-amino	H	(Z)-3-{1-[4-(N-piperidinomethylcarbonyl-N-methyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-2-ylsulphonylamino)-2-indolinone	236-237

Example 98

(Z)-3-[1-(4-piperidinomethyl-phenylamino)-1-phenyl-methylidene]-5-methylsulphonylamino-2-indolinone

a. 1-acetyl-3-(1-ethoxy-1-phenyl-methylidene)-5-nitro-2-indolinone

0 2 g (0 9 mmol) of 1-acetyl-5-nitro-2-indolinone and 0 6 g (2 7 mmol) of triethyl orthobenzoate are heated to 100°C in 2 ml of acetic acid anhydride for 1 5 hours After cooling the mixture is combined with ether and the precipitate formed is suction filtered.
Yield: 0 2 g (66 % of theory),
Melting point: 244-250°C
R_f value: 0 7 (silica gel; ethyl acetate/cyclohexane = 3:2)

b. (Z)-1-acetyl-3-[1-(4-piperidinomethyl-phenylamino)-1-phenyl-methylidene]-5-nitro-2-indolinone

3 g (8 5 mmol) of 1-acetyl-3-(1-ethoxy-1-phenyl-methylidene)-5-nitro-2-indolinone and 1 9 g (10 mmol) of 4-piperidinomethyl-aniline are heated to 90°C in 30 ml of DMF for 3 5 hours After cooling to ambient temperature the reaction solution is poured onto ice water and extracted with ethyl acetate The combined organic extracts are dried and evaporated down The residue is triturated with ether and suction filtered
Yield: 3 5 g (82 % of theory),
R_f value: 0 6 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)
Melting point: 165°C

c. (Z)-1-acetyl-3-[1-(4-piperidinomethyl-phenylamino)-1-phenyl-methylidene]-5-amino-2-indolinone

Prepared analogously to Example VIIb from (Z)-1-acetyl-3-[1-(4-piperidinomethyl-phenylamino)-1-phenyl-methylidene]-5-nitro-2-indolinone by catalytic reduction over Raney nickel in dichloromethane/methanol (1:1)
Yield: 99 % of theory,
R_f value: 0 5 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)
Melting point: 278-281°C
$C_{29}H_{30}N_4O_2$ (466 59)
Mass spectrum: $(M+H)^+ = 467$

d. (Z)-3-[1-(4-piperidinomethyl-phenylamino)-1-phenyl-methylidene]-5-methylsulphonylamino-2-indolinone

466 mg (1 mmol) of (Z)-1-acetyl-3-[1-(4-piperidinomethyl-phenylamino)-1-phenyl-methylidene]-5-amino-2-indolinone are suspended in 15 ml of pyridine, combined with 0 2 ml (2 3 mmol) of methanesulphonic acid chloride and stirred for 1 5 hours Then 6 ml of 1 N sodium hydroxide solution are added After 1 hour 1 ml of piperidine is added and the mixture is stirred overnight The reaction solution is poured onto water and the precipitate formed is suction filtered The residue is stirred with ether, suction filtered and dried

Yield: 290 mg (58 % of theory),

R_f value: 0 4 (silica gel; dichloromethane/methanol/ammonia = 9:1:0 1)

Melting point: 266°C

$C_{28}H_{30}N_4O_3S$ (502 64)

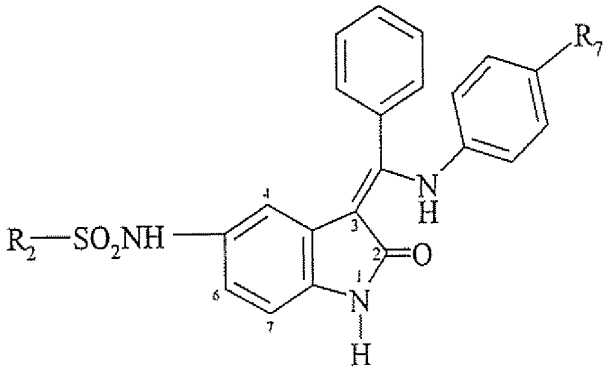
Mass spectrum: $(M+H)^+ = 503$

Calc :	C 66 91	H 6 02	N 11 15
Found:	C 66 49	H 6 06	N 11 01

Examples 99 to 151

Using the intermediate products prepared in Examples I to XIII , the compounds of formula IB of Examples 99 to 151 listed in Table II are prepared analogously to Example 98 Hydrochlorides or dihydrochlorides are obtained according to the following general working method: The starting compound is dissolved in dichloromethane and combined with ether/HCl The precipitate formed is suction filtered and dried

Table II



(IB),

Example	R_2	R_7	chemical name	Melting point (°C)
99	ethyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone	235
100	ethyl	methoxy	(Z)-3-[1-(4-methoxyphenylamino)-1-phenyl-methylidene]-5-ethyl-sulphonylamino-2-indolinone	283
101	isopropyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-isopropylsulphonylamino-2-indolinone	205
102	4-chlorophenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(4-chlorophenylsulphonylamino)-2-indolinone	251-253

103	3-chlorophenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-chlorophenylsulphonylamino)-2-indolinone	275-277
104	naphthalin-1-yl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(naphthalin-1-ylsulphonylamino)-2-indolinone	236-237
105	4-methylphenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(4-methylphenylsulphonylamino)-2-indolinone	267-269
106	3-methylphenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-methylphenylsulphonylamino)-2-indolinone	269-271
107	3-methoxyphenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-methoxyphenylsulphonylamino)-2-indolinone	241-245
108	4-methoxyphenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(4-methoxyphenylsulphonylamino)-2-indolinone	253-256
109	2,4,6-trimethylphenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(2,4,6-trimethylphenylsulphonylamino)-2-indolinone	224

110	4-nitrophenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(4-nitrophenylsulphonylamino)-2-indolinone	276
111	naphthalin-2-yl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(naphthalin-2-ylsulphonylamino)-2-indolinone	234
112	3-nitrophenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-nitrophenylsulphonylamino)-2-indolinone	145
113	quinolin-8-yl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(quinolin-8-ylsulphonylamino)-2-indolinone	279
114	2-chlorophenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(2-chlorophenylsulphonylamino)-2-indolinone	275
115	2-nitrophenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(2-nitrophenylsulphonylamino)-2-indolinone	140
116	3-cyanophenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-cyanophenylsulphonylamino)-2-indolinone	248

117	3,5-dimethylisoxazol-4-yl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(3,5-dimethylisoxazol-4-ylsulphonylamino)-2-indolinone	240
118	E-2-phenylethenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-((E)-2-phenylethenylsulphonylamino)-2-indolinone	248
119	1-methyl-1H-imidazol-4-yl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(1-methyl-1H-imidazol-4-ylsulphonylamino)-2-indolinone-dihydrochloride	230
120	cyclopropyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-cyclopropylsulphonylamino-2-indolinone	231
121	2-cyanophenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(2-cyanophenylsulphonylamino)-2-indolinone	239
122	pyridin-2-yl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-2-ylsulphonylamino)-2-indolinone	263
123	phenyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-	262

			phenylsulphonylamino-2-indolinone	
124	benzyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-benzylsulphonylamino-2-indolinone	254
125	propyl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-propylsulphonylamino-2-indolinone	188
126	benzyl	N-(2-dimethylami-no-ethyl)-N-methyl-sulphonyl-amino	(Z)-3-{1-[4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-benzylsulphonylamino-2-indolinone	163-164
127	isopropyl	2-dimethylamino-ethyl	(Z)-3-{1-[4-(2-dimethylamino-ethyl)-phenylamino]-1-phenyl-methylidene}-5-isopropylsulphonylamino-2-indolinone	220
128	propyl	2-dimethylamino-ethyl	(Z)-3-{1-[4-(2-dimethylamino-ethyl)-phenylamino]-1-phenyl-methylidene}-5-propylsulphonylamino-2-indolinone	239-240
129	propyl	N-benzyl-N-methyl-aminomethyl	(Z)-3-{1-[4-(N-benzyl-N-methyl-aminomethyl)-phenylamino]-1-phenyl-methylidene}-5-propylsulphonylamino-2-indolinone	195-197

130	methyl	N-benzyl-N-methyl-aminomethyl	(Z)-3-{1-[4-(N-benzyl-N-methyl-aminomethyl)-phenylamino]-1-phenyl-methylidene}-5-methylsulphonylamino-2-indolinone	241-242
131	phenyl	N-benzyl-N-methyl-aminomethyl	(Z)-3-{1-[4-(N-benzyl-N-methyl-aminomethyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	148-150
132	benzyl	N-benzyl-N-methyl-aminomethyl	(Z)-3-{1-[4-(N-benzyl-N-methyl-aminomethyl)-phenylamino]-1-phenyl-methylidene}-5-benzylsulphonylamino-2-indolinone	200-204
133	benzyl	2-dimethylamino-ethyl	(Z)-3-{1-[4-(2-dimethylamino-ethyl)-phenylamino]-1-phenyl-methylidene}-5-benzylsulphonylamino-2-indolinone-hydrochloride	260-262
134	pyridin-3-yl	piperidinomethyl	(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylphenylsulphonylamino)-2-indolinone	236
135	3-nitrophenyl	dimethylaminomethyl	(Z)-3-{1-[4-(dimethylaminomethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-nitrophenylsulphonylamino)-2-indolinone	246-247
136	3-methoxy-phenyl	dimethylaminomethyl	(Z)-3-{1-[4-(dimethylaminomethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-methoxyphenylsulphonylamino)-2-indolinone	259-260

137	3-nitrophenyl	dimethylaminomethyl amino	(Z)-3-{1-[4-(N-methyl-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(3-nitrophenylsulphonylamino)-2-indolinone	298-300
138	2-nitrophenyl	N-methyl-N-acetyl-amino	(Z)-3-{1-[4-(N-methyl-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(2-nitrophenylsulphonylamino)-2-indolinone	295-297
139	3-cyanophenyl	N-methyl-N-acetyl-amino	(Z)-3-{1-[4-(N-methyl-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(3-cyanophenylsulphonylamino)-2-indolinone	330-332
140	3-nitrophenyl	4-methyl-piperazinomethyl	(Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-nitrophenylsulphonylamino)-2-indolinone	166-167
141	pyridin-2-yl	pyrrolidin-1-ylmethyl	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-2-ylsulphonylamino)-2-indolinone	261
142	cyclopropyl	pyrrolidin-1-ylmethyl	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-cyclopropylsulphonylamino-2-indolinone	256
143	propyl	pyrrolidin-1-ylmethyl	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-propylsulphonylamino-2-indolinone	247

144	ethyl	pyrrolidin-1-ylmethyl	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone	245
145	methyl	pyrrolidin-1-ylmethyl	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-methylsulphonylamino-2-indolinone	248
146	2-fluorophenyl	pyrrolidin-1-ylmethyl	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-(2-fluorophenylsulphonylamino)-2-indolinone	247
147	4-fluorophenyl	pyrrolidin-1-ylmethyl	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-(4-fluorophenylsulphonylamino)-2-indolinone	244
148	3-fluorophenyl	pyrrolidin-1-ylmethyl	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-fluorophenylsulphonylamino)-2-indolinone	257
149	2-nitrophenyl	pyrrolidin-1-ylmethyl	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-(2-nitrophenylsulphonylamino)-2-indolinone	185
150	3-cyanophenyl	pyrrolidin-1-ylmethyl	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-cyanophenylsulphonylamino)-2-indolinone	249
151	2-cyanophenyl	pyrrolidin-1-ylmethyl	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-(2-cyanophenylsulphonylamino)-2-indolinone	232

Example 152

(Z)-3-[1-(4-ethoxycarbonylmethyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone

a. 3-(1-ethoxy-1-phenyl-methylidene)-5-phenylsulphonylamino-2-indolinone

8 ml of 4 N sodium hydroxide solution are added to a solution of 4 0 g (8 mmol) of 1-acetyl-3-(1-ethoxy-1-phenyl-methylidene)-5-(N-acetyl-N-phenylsulphonyl-amino)-2-indolinone (Example 1e) in a mixture of 20 ml of dichloromethane and 20 ml of ethanol and the resulting mixture is stirred for 20 minutes at ambient temperature It is then evaporated down to about 10 ml and 150 ml of water are added The pH is adjusted to 8-9 with 1 N hydrochloric acid The precipitate formed is suction filtered, washed with water, isopropanol and ether, then dried *in vacuo*

Yield: 6 6 g (82% of theory),

Melting point: 292-294 °C

R_f value: 0.4 (silica gel; dichloromethane/methanol/NH_4OH = 9:1:0 1)

$C_{23}H_{20}N_2O_4S$ (420 49)

Mass spectrum: $(M+H)^+ = 421$, $(M-H)^- = 419$

b. (Z)-3-[1-(4-ethoxycarbonylmethyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone

0 84 g (2 mmol) of 3-(1-ethoxy-1-phenyl-methylidene)-5-phenylsulphonylamino-2-indolinone and 0 39 g (2 2 mmol) of 4-ethoxycarbonylmethyl-aniline are dissolved in 10 ml of DMF. The mixture is heated to 140°C for 5 hours Then water is added while the mixture is cooled with ice and stirred for 1 hour at ambient temperature The precipitate formed is suction filtered, washed with water, a little isopropanol and ether, then dried *in vacuo*

Yield: 0 95 g (86 % of theory),

Melting point: 248-249°C

$C_{31}H_{27}N_3O_5S$ (553 64)

Mass spectrum: $M^+ = 553$, $(M-H)^- = 552$

Example 153

(Z)-3-[1-(4-carboxymethyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone

720 mg (1 3 mmol) of (Z)-3-[1-(4-ethoxycarbonylmethyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone are dissolved in a mixture of 20 ml of methanol and 20 ml of dichloromethane 4 ml of 1 N sodium hydroxide solution are added and the mixture is stirred for 18 hours at ambient temperature and for another 1 hour at 40°C The reaction solution is evaporated down to half the volume and the pH is adjusted to 4-5 with 1 N hydrochloric acid The precipitate formed is suction filtered, washed with water, a little isopropanol and ether

Yield: 620 mg (91% of theory),

Melting point: 305-306°C

$C_{29}H_{23}N_3O_5S$ (525 59)

Mass spectrum: $(M-H)^-$ = 524

Example 154

(Z)-3-{1-[4-(benzylaminocarbonylmethyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone

A solution of 315 mg (0 6 mmol) of (Z)-3-[1-(4-carboxymethyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone, 85 mg (0 8 mmol) of benzylamine, 212 mg (0 66 mmol) of TBTU and 1 ml of N-ethyl-N,N-diisopropyl-amine in 5 ml of DMF is stirred for 3 hours at ambient temperature Then 50 ml of water are added The yellow precipitate formed is suction filtered, washed with water, a little isopropanol and ether, then dried *in vacuo*

Yield: 0 3 mg (81 % of theory),

Melting point: 219-220°C

$C_{36}H_{30}N_4O_4S$ (614 73)

Mass spectrum: $(M+Na)^+$ = 637, $(M-H)^-$ = 613

Example 155

(Z)-3-{1-[4-(N-(aminocarbonylmethyl)-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone

A solution of 250 mg (0 4 mmol) of (Z)-3-[1-(4-(N-carboxymethyl-N-methylsulphonyl-amino)-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone and 82 mg (0 4 mmol) of CDI in 5 ml of DMF is stirred for 1 hour at 50°C 1 ml of condensed ammonia is added and the mixture is stirred for 5 hours at ambient temperature Then water is added The yellow precipitate is suction filtered, washed with water, a little isopropanol and ether, then dried *in vacuo*

Yield: 190 mg (76 % of theory)

Melting point: 216-217°C

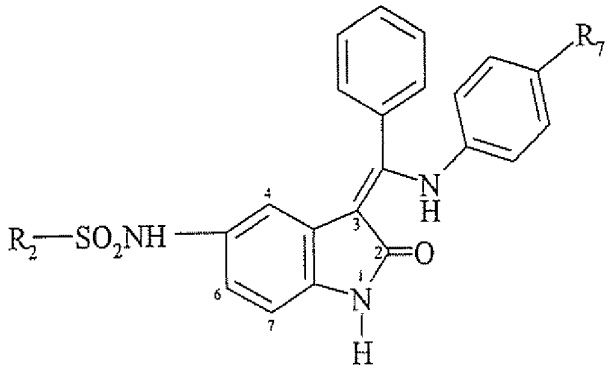
$C_{30}H_{27}N_5O_6S_2$ (617 71)

Mass spectrum: $(M+Na)^+ = 640$, $(M-H)^- = 616$

Examples 156 to 170

Using the intermediate products prepared in Examples I to XIII , the compounds of formula IB of Examples 156 to 170 listed in Table III are prepared analogously to Examples 152 to 155

Table III



(IB),

Example	R_2	R_7	chemical name	Melting point (°C)
156	phenyl	methoxycarbonyl	(Z)-3-[1-(4-methoxycarbonyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	304-305
157	phenyl	carboxy	(Z)-3-[1-(4-carboxyphenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	312-313
158	phenyl	benzylaminocarbonyl	(Z)-3-{1-[4-(benzylaminocarbonyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	269-270
159	methyl	methoxycarbonyl	(Z)-3-[1-(4-methoxycarbonyl-phenylamino)-1-phenyl-methylidene]-5-methylsulphonylamino-2-indolinone	> 270
160	methyl	carboxy	(Z)-3-[1-(4-carboxyphenylamino)-1-phenyl-methylidene]-5-methylsulphonylamino-2-indolinone	> 270
161	phenyl	N-carboxymethyl-N-acetyl-	(Z)-3-{1-[4-(N-carboxymethyl-N-acetyl-amino)-phenylamino]-	190-191

		amino	1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	
162	phenyl	N-aminocarbonylmethyl-N-acetyl-amino	(Z)-3-{1-[4-(N-(aminocarbonylmethyl)-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	150 (decomp.)
163	phenyl	N-methylaminocarbonyl-methyl-N-acetyl-amino	(Z)-3-{1-[4-(N-methylaminocarbonylmethyl-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	150 (decomp.)
164	phenyl	N-dimethylaminocarbonyl-methyl)-N-acetyl-amino)	(Z)-3-{1-[4-(N-dimethylaminocarbonylmethyl-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	150 (decomp.)
165	phenyl	N-carboxymethyl-N-ethylsulphonyl-amino	(Z)-3-{1-[4-(N-carboxymethyl-N-ethylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	231-235
166	phenyl	N-[N-(2-dimethylamino-ethyl)-N-methyl-amino-carbonylmethyl]-N-ethylsulphonyl-amino	(Z)-3-{1-[4-(N-(N-(2-dimethylamino-ethyl)-N-methyl-aminocarbonylmethyl)-N-ethylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	147-151
167	phenyl	N-[(2-dimethylamino-ethyl)-aminocarbonylmethyl]-N-ethylsulphonyl-amino	(Z)-3-{1-[4-(N-((2-dimethylamino-ethyl)-aminocarbonylmethyl)-N-ethylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	142-147

168	phenyl	N-carboxylmethyl-N-methylsulphonyl-amino	(Z)-3-{1-[4-(N-carboxylmethyl-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	215-216
169	phenyl	N-methylaminocarbonyl-methyl-N-methylsulphonyl-amino	(Z)-3-{1-[4-(N-methylaminocarbonylmethyl-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	150 (decomp.)
170	phenyl	N-dimethylamino-carbonylmethyl-N-methylsulphonyl-amino	(Z)-3-{1-[4-(N-dimethylaminocarbonylmethyl-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	150 (decomp.)

Examples 171 to 206

The compounds of formula IB of Examples 171 to 196 listed in the following Table IV are obtained from compounds of the abovementioned Examples 1 to 170 by the following general methods A to E:

A: Cleaving of tert.butoxycarbonyl:

0 6 mmol of the starting compound are dissolved in 5 ml of dichloromethane 10 ml of ethyl acetate/HCl are added and the mixture is stirred for 2 hours at ambient temperature Then a basic pH is obtained by the addition of sodium hydroxide solution The organic phase is washed with water, dried over sodium sulphate and the solvent is eliminated *in vacuo* In order to prepare hydrochlorides the addition of sodium hydroxide solution is omitted In order to prepare hydrotrifluoroacetate, trifluoroacetic acid is added to the solution of the starting compound

B: Cleaving of benzyl:

1 5 mmol of the starting compound are dissolved in 20 ml of dichloromethane/methanol (1:1). 100 mg of palladium/charcoal (10%) and 1 5 ml of 1 N hydrochloric acid are added and the mixture is then hydrogenated in a hydrogen atmosphere at 50 psi The catalyst is suction filtered and the filtrate is evaporated to dryness The residue is chromatographed on silica gel (dichloromethane/methanol/NH_4OH, 9:1:0 1)

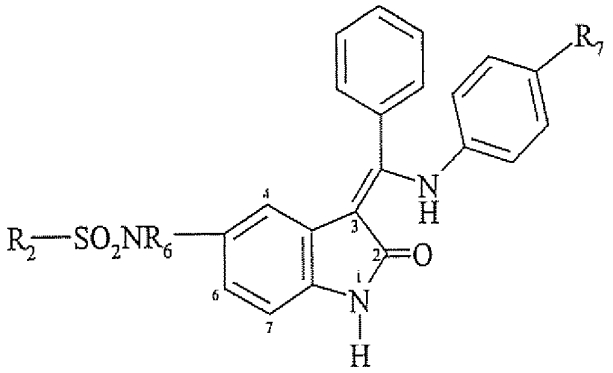
C: hydrogenation of cyano to CH_2NH_2:

0 5 mmol of the starting compound are dissolved in 20 ml of methanolic ammonia solution and combined with Raney nickel The mixture is hydrogenated in a hydrogen atmosphere of 50 psi, then the catalyst is suction filtered and the solvent is eliminated *in vacuo* The residue is chromatographed on silica gel (dichloromethane/methanol/NH_4OH, 9:1:0 1)

D: hydrogenation of nitro to amino:

0 2 mmol of the starting compound are dissolved in 20 ml of ethyl acetate/methanol (1:1) Then the mixture is hydrogenated analogously to Method C over Raney nickel. The residue is optionally chromatographed on silica gel (dichloromethane/methanol/NH_4OH, 9:1:0 1).

Table IV



(IB),

Example	method	R_2	R_6	R_7	chemical name	Melting point (°C)
171	A	phenyl	H	amino	(Z)-3-[1-(4-aminophenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	220-223
172	A	phenyl	H	piperazinomethyl	(Z)-3-[1-(4-piperazinomethyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	380 (decomp.)
173	A	3-methoxyphenyl	H	aminomethyl	(Z)-3-[1-(4-aminomethyl-phenylamino)-1-phenyl-methylidene]-5-(3-methoxyphenylsulphonylamino)-2-indolinone-hydrochloride	200 (decomp.)
174	A	benzyl	H	aminomethyl	(Z)-3-[1-(4-aminomethyl-phenylamino)-1-phenyl-methylidene]-5-benzylsulphonylamino)-2-indolinone-hydrochloride	200 (decomp.)
175	A	3-nitrophenyl	H	aminomethyl	(Z)-3-[1-(4-aminomethyl-phenylamino)-1-phenyl-methylidene]-5-(3-nitrophenylsulphonylamino)-2-indolinone-hydrochloride	215 (decomp.)
176	A	phenyl	H	ethylaminomethy	(Z)-3-[1-(4-ethylaminomethyl-phenylamino)-1-phenyl-	230

				l	methylidene]-5-phenylsulphonylamino-2-indolinone-hydrotrifluoroacetat	
177	A	phenyl	H	propylamino-methyl	(Z)-3-[1-(4-propylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone-hydrotrifluoroacetate	238
178	A	phenyl	H	butylamino-methyl	(Z)-3-[1-(4-butylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone-hydrotrifluoroacetate	260
179	B	phenyl	H	N-(2-methylamino-ethyl)-N-acetyl-amino	(Z)-3-{1-[4-(N-(2-methylamino-ethyl)-N-acetyl-amino)-phenyl-amino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	180 (decomp.)
180	B	phenyl	H	N-(2-methylamino-ethyl)-N-propionyl-amino	(Z)-3-{1-[4-(N-(2-methylamino-ethyl)-N-propionyl-amino)-phenyl-amino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone	214
181	C	3-aminomethyl-phenyl	H	piperidinomethyl	(Z)-3-[1-(4-piperidinomethyl-phenylamino]-1-phenyl-methylidene]-5-(3-aminomethyl-phenylsulphonylamino)-2-indolinone	237
182	C	phenyl	H	aminomethyl	(Z)-3-[1-(4-aminomethyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone	230-232

183	C	2-aminomethyl-phenyl	H	piperidinomethyl	(Z)-3-[1-(4-piperidinomethyl-phenylamino]-1-phenyl-methylidene]-5-(2-aminomethyl-phenylsulphonylamino)-2-indolinone	237
184	C	3-aminomethyl-phenyl	H	N-methyl-N-acetyl-amino	(Z)-3-{1-[4-(N-methyl-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(3-aminomethyl-phenylsulphonylamino)-2-indolinone	277-279
185	C	3-aminomethyl-phenyl	H	pyrrolidin-1-ylmethyl	(Z)-3-[1-(4-pyrrolidin-1-ylmethyl-phenylamino]-1-phenyl-methylidene]-5-(3-aminomethyl-phenylsulphonylamino)-2-indolinone	261
186	D	4-aminophenyl	H	piperidinomethyl	(Z)-3-[1-(4-piperidinomethyl-phenylamino)-1-phenyl-methylidene]-5-(4-aminophenylsulphonylamino)-2-indolinone	279
187	D	3-aminophenyl	H	piperidinomethyl	(Z)-3-[1-(4-piperidinomethyl-phenylamino)-1-phenyl-methylidene]-5-(3-aminophenylsulphonylamino)-2-indolinone	240
188	D	2-aminophenyl	H	piperidinomethyl	(Z)-3-[1-(4-piperidinomethyl-phenylamino]-1-phenyl-methylidene]-5-(2-aminophenylsulphonylamino)-2-indolinone-hydrochloride	220 (decomp.)
189	D	3-aminophenyl	H	dimethylaminomethyl	(Z)-3-[1-(4-dimethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-(3-aminophenylsulphonylamino)-2-indolinone	250 (decomp.)
190	D	3-aminophenyl	H	N-methyl-N-acetyl-amino	(Z)-3-{1-[4-(N-methyl-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(3-aminophenylsulphonylamino)-2-indolinone	207-209
191	D	2-aminophenyl	H	N-methyl-N-acetyl-amino	(Z)-3-{1-[4-(N-methyl-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-(2-aminophenylsulphonylamino)-2-indolinone	295-298

192	D	3-aminophenyl	H	pyrrolidin-1-ylmethyl	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino)-1-phenyl-methylidene}-5-(3-aminophenylsulphonylamino)-2-indolinone	242
193	D	3-aminophenyl	H	(2,6-dimethylpiperidino)-methyl	(Z)-3-{1-[4-((2,6-dimethylpiperidino)-methyl)-phenylamino]-1-phenyl-methylidene}-5-(3-aminophenylsulphonylamino)-2-indolinone	150 (decomp.)
194	D	3-aminophenyl	H	aminomethyl	(Z)-3-[1-(4-aminomethyl-phenylamino)-1-phenyl-methylidene]-5-(3-aminophenylsulphonylamino)-2-indolinone	257
195	D	3-aminophenyl	H	4-methylpiperazinomethyl	(Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-aminophenylsulphonylamino)-2-indolinone	217-218
196	D	2-aminophenyl	H	pyrrolidin-1-ylmethyl	(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino)-1-phenyl-methylidene}-5-(2-aminophenylsulphonylamino)-2-indolinone	260

Example 197

(Z)-3-{1-[4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-phenylamino)-1-phenyl-methylidene}-5-(N-methyl-N-phenylsulphonyl-amino)-2-indolinone

a. (Z)-1-acetyl-3-(1-ethoxy-1-phenyl-methylidene)-5-(N-methyl-N-phenylsulphonyl-amino)-2-indolinone

10 g (20 mmol) of 1-acetyl-3-(1-ethoxy-1-phenyl-methylidene)-5-(N-acetyl-N-phenylsulphonyl-amino)-2-indolinone (Example 1e) are dissolved in 150 ml of DMSO and combined with 2 2 g (20 mmol) of potassium tert butoxide with stirring. After 15 minutes' stirring 1 9 ml (31 mmol) of iodomethane are added The mixture is stirred for 3 hours at ambient temperature Then another 2 2 g (20 mmol) of potassium tert butoxide and 1 ml (16 mmol) of iodomethane are added The mixture is stirred for 18 hours at ambient temperature Then water is added The reaction mixture is extracted with ethyl acetate The organic phase is washed with water, dried over magnesium sulphate and evaporated to dryness The residue is chromatographed on silica gel (petroleum ether/dichloromethane, 7:3)

Yield: 2 7 g (28% of theory)

R_f value: 0.65 (silica gel; dichloromethane/petroleum ether = 8:2)

$C_{26}H_{24}N_2O_5S$ (476 56)

Mass spectrum: $(M+Na)^+ = 499$

b. (Z)-3-{1-[4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-phenylamino)-1-phenyl-methylidene}-5-(N-methyl-N-phenylsulphonyl-amino)-2-indolinone

Prepared analogously to Example 1f from 350 mg (0 73 mmol) of (Z)-1-acetyl-3-(1-ethoxy-1-phenyl-methylidene)-5-(N-methyl-N-phenylsulphonyl-amino)-2-indolinone and 257 mg (1 mmol) of 4-[N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino]-aniline in DMF and subsequent treatment with sodium hydroxide solution

Yield: 380 mg (80% of theory)

R_f value: 0 5 (silica gel; dichloromethane/methanol/NH_4OH = 9:1:0 1)

$C_{33}H_{35}N_5O_5S_2$ (645 80)

Mass spectrum: $M^+ = 645$

Calc :	C 61 38	H 5.46	N 10 84
Found:	C 61 09	H 5.45	N 10 82

The following compounds of Examples 198 to 200 are prepared analogously to Example 197 using the intermediate products prepared in Examples I to XIII:

Example 198

(Z)-3-{1-[4-(N-(2-dimethylamino-ethyl)-N-acetyl-amino)-phenylamino)-1-phenyl-methylidene}-5-(N-methyl-N-phenylsulphonyl-amino)-2-indolinone

Melting point: 217°C

R_f value: 0.5 (silica gel; dichloromethane/methanol/NH_4OH = 9:1:0.1)

$C_{34}H_{35}N_5O_4S$ (609.75)

Mass spectrum: $(M+H)^+$ = 610

Calc.:	C 66.97	H 5.79	N 11.49
Found:	C 66.92	H 5.78	N 11.39

Example 199

(Z)-3-{1-[4-(N-methyl-N-piperidinomethylcarbonyl-amino)-phenylamino)-1-phenyl-methylidene}-5-(N-methyl-N-phenylsulphonyl-amino)-2-indolinone

Melting point: 160°C

R_f value: 0.65 (silica gel; dichloromethane/methanol/NH_4OH = 9:1:0.1)

$C_{36}H_{37}N_5O_4S$ (635.79)

Mass spectrum: $(M+H)^+$ = 636

Example 200

(Z)-3-[1-(3-dimethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-(N-methyl-N-phenylsulphonyl-amino)-2-indolinone

Melting point: 226°C

R_f value: 0.75 (silica gel; dichloromethane/methanol/NH_4OH = 9:1:0.1)

$C_{31}H_{30}N_4O_3S$ (538 67)

Mass spectrum: $(M+H)^+$ = 539

The following compounds may be obtained analogously to the foregoing Examples:

(1) (Z)-3-[1-(3-dimethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-ethylsulphonylamino-2-indolinone, melting point 222-224 °C

(2) (Z)-3-{1-[4-(2-dimethylaminoethyl)-phenylamino]-1-phenyl-methylidene}-5-methylsulphonylamino-2-indolinone

(3) (Z)-3-[1-(4-diethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-methylsulphonylamino-2-indolinone

(4) (Z)-3-[1-(4-dipropylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-methylsulphonylamino-2-indolinone

(5) (Z)-3-[1-(4-hexamethyleneiminomethyl-phenylamino)-1-phenyl-methylidene]-5-methylsulphonylamino-2-indolinone

(6) (Z)-3-{1-[4-(4-methylpiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-methylsulphonylamino-2-indolinone

(7) (Z)-3-[1-(4-morpholinomethyl-phenylamino)-1-phenyl-methylidene]-5-methylsulphonylamino-2-indolinone

(8) (Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-methylsulphonylamino-2-indolinone

(9) (Z)-3-[1-(4-piperazinomethyl-phenylamino)-1-phenyl-methylidene]-5-methylsulphonylamino-2-indolinone

(10) (Z)-3-{1-[4-(2,6-dimethylpiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-methylsulphonylamino-2-indolinone

(11) (Z)-3-[1-(4-dipropylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-ethylsulphonylamino-2-indolinone

(12) (Z)-3-[1-(4-hexamethyleneiminomethyl-phenylamino)-1-phenyl-methylidene]-5-ethylsulphonylamino-2-indolinone

(13) (Z)-3-{1-[4-(4-methylpiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone

(14) (Z)-3-[1-(4-morpholinomethyl-phenylamino)-1-phenyl-methylidene]-5-ethylsulphonylamino-2-indolinone

(15) (Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone

(16) (Z)-3-[1-(4-piperazinomethyl-phenylamino)-1-phenyl-methylidene]-5-ethylsulphonylamino-2-indolinone

(17) (Z)-3-{1-[4-(2,6-dimethylpiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone

(18) (Z)-3-[1-(4-piperazinomethyl-phenylamino)-1-phenyl-methylidene]-5-propylsulphonylamino-2-indolinone

(19) (Z)-3-{1-[4-(2,6-dimethylpiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-propylsulphonylamino-2-indolinone

(20) (Z)-3-[1-(4-diethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-propylsulphonylamino-2-indolinone

(21) (Z)-3-[1-(4-dipropylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-propylsulphonylamino-2-indolinone

(22) (Z)-3-[1-(4-hexamethyleneiminomethyl-phenylamino)-1-phenyl-methylidene]-5-propylsulphonylamino-2-indolinone

(23) (Z)-3-{1-[4-(4-methylpiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-propylsulphonylamino-2-indolinone

(24) (Z)-3-[1-(4-morpholinomethyl-phenylamino)-1-phenyl-methylidene]-5-propylsulphonylamino-2-indolinone

(25) (Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-propylsulphonylamino-2-indolinone

(26) (Z)-3-[1-(4-piperazinomethyl-phenylamino)-1-phenyl-methylidene]-5-cyclopropylsulphonylamino-2-indolinone

(27) (Z)-3-{1-[4-(2,6-dimethylpiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-cyclopropylsulphonylamino-2-indolinone

(28) (Z)-3-[1-(4-dimethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-cyclopropylsulphonylamino-2-indolinone

(29) (Z)-3-{1-[4-(2-dimethylaminoethyl)-phenylamino]-1-phenyl-methylidene}-5-cyclopropylsulphonylamino-2-indolinone

(30) (Z)-3-[1-(4-diethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-cyclopropylsulphonylamino-2-indolinone

(31) (Z)-3-[1-(4-dipropylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-cyclopropylsulphonylamino-2-indolinone

(32) (Z)-3-[1-(4-hexamethyleneiminomethyl-phenylamino)-1-phenyl-methylidene]-5-cyclopropylsulphonylamino-2-indolinone

(33) (Z)-3-{1-[4-(4-methylpiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-cyclopropylsulphonylamino-2-indolinone

(34) (Z)-3-[1-(4-morpholinomethyl-phenylamino)-1-phenyl-methylidene]-5-cyclopropylsulphonylamino-2-indolinone

(35) (Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-cyclopropylsulphonylamino-2-indolinone

(36) (Z)-3-[1-(4-piperazinomethyl-phenylamino)-1-phenyl-methylidene]-5-trifluoromethylsulphonylamino-2-indolinone

(37) (Z)-3-{1-[4-(2,6-dimethylpiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-trifluoromethylsulphonylamino-2-indolinone

(38) (Z)-3-[1-(4-dimethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-trifluoromethylsulphonylamino-2-indolinone

(39) (Z)-3-{1-[4-(2-dimethylaminoethyl)-phenylamino]-1-phenyl-methylidene}-5-trifluoromethylsulphonylamino-2-indolinone

(40) (Z)-3-[1-(4-diethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-trifluoromethylsulphonylamino-2-indolinone

(41) (Z)-3-[1-(4-dipropylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-trifluoromethylsulphonylamino-2-indolinone

(42) (Z)-3-{1-[4-(pyrrolidin-1-yl)-methyl-phenylamino]-1-phenyl-methylidene}-5-trifluoromethylsulphonylamino-2-indolinone

(43) (Z)-3-[1-(4-piperidinomethyl-phenylamino)-1-phenyl-methylidene]-5-trifluoromethylsulphonylamino-2-indolinone

(44) (Z)-3-[1-(4-hexamethyleneiminomethyl-phenylamino)-1-phenyl-methylidene]-5-trifluoromethylsulphonylamino-2-indolinone

(45) (Z)-3-{1-[4-(4-methylpiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-trifluoromethylsulphonylamino-2-indolinone

(46) (Z)-3-[1-(4-morpholinomethyl-phenylamino)-1-phenyl-methylidene]-5-trifluoromethylsulphonylamino-2-indolinone

(47) (Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-trifluoromethylsulphonylamino-2-indolinone

(48) (Z)-3-[1-(4-piperazinomethyl-phenylamino)-1-phenyl-methylidene]-5-isopropylsulphonylamino-2-indolinone

(49) (Z)-3-{1-[4-(2,6-dimethylpiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-isopropylsulphonylamino-2-indolinone

(50) (Z)-3-[1-(4-dimethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-isopropylsulphonylamino-2-indolinone

(51) (Z)-3-[1-(4-diethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-isopropylsulphonylamino-2-indolinone

(52) (Z)-3-[1-(4-dipropylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-isopropylsulphonylamino-2-indolinone

(53) (Z)-3-{1-[4-(pyrrolidin-1-yl)-methyl-phenylamino]-1-phenyl-methylidene}-5-isopropylsulphonylamino-2-indolinone

(54) (Z)-3-[1-(4-hexamethyleneiminomethyl-phenylamino)-1-phenyl-methylidene]-5-isopropylsulphonylamino-2-indolinone

(55) (Z)-3-{1-[4-(4-methylpiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-isopropylsulphonylamino-2-indolinone

(56) (Z)-3-[1-(4-morpholinomethyl-phenylamino)-1-phenyl-methylidene]-5-isopropylsulphonylamino-2-indolinone

(57) (Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-isopropylsulphonylamino-2-indolinone

(58) (Z)-3-[1-(4-piperazinomethyl-phenylamino]-1-phenyl-methylidene}-5-isopropylsulphonylamino-2-indolinone

(59) (Z)-3-{1-[4-(2,6-dimethylpiperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-isopropylsulphonylamino-2-indolinone

Example 201

Dry ampoule containing 75 mg of active substance per 10 ml

Composition:

Active substance	75 0 mg
Mannitol	50 0 mg
water for injections	ad 10 0 ml

Preparation:
Active substance and mannitol are dissolved in water After packaging the solution is freeze-dried To produce the solution ready for use, the product is dissolved in water for injections

Example 202

Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

Active substance	35 0 mg
Mannitol	100 0 mg
water for injections	ad 2 0 ml

Preparation:
Active substance and mannitol are dissolved in water After packaging, the solution is freeze-dried.

To produce the solution ready for use, the product is dissolved in water for injections.

Example 203

Tablet containing 50 mg of active substance

Composition.

(1) Active substance	50 0 mg
(2) Lactose	98 0 mg
(3) Maize starch	50 0 mg
(4) Polyvinylpyrrolidone	15 0 mg
(5) Magnesium stearate	2.0 mg
	215 0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.
Diameter of the tablets: 9 mm

Example 204

Tablet containing 350 mg of active substance

Preparation:

(1) Active substance	350.0 mg
(2) Lactose	136 0 mg
(3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	600 0 mg

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4) (5) is added to the dried granulated material From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side
Diameter of the tablets: 12 mm

Example 205

Capsules containing 50 mg of active substance

Composition:

(1) Active substance	50 0 mg
(2) Dried maize starch	58 0 mg
(3) Powdered lactose	50 0 mg
(4) Magnesium stearate	2.0 mg
	160 0 mg

Preparation:
(1) is triturated with (3) This trituration is added to the mixture of (2) and (4) with vigorous mixing

This powder mixture is packed into size 3 hard gelatine capsules in a capsule filling machine

Example 206

Capsules containing 350 mg of active substance

Composition:

(1) Active substance	350 0 mg
(2) Dried maize starch	46 0 mg
(3) Powdered lactose	30 0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

Preparation:

(1) is triturated with (3) This trituration is added to the mixture of (2) and (4) with vigorous mixing

This powder mixture is packed into size 0 hard gelatine capsules in a capsule filling machine

Example 207

Suppositories containing 100 mg of active substance

1 suppository contains:

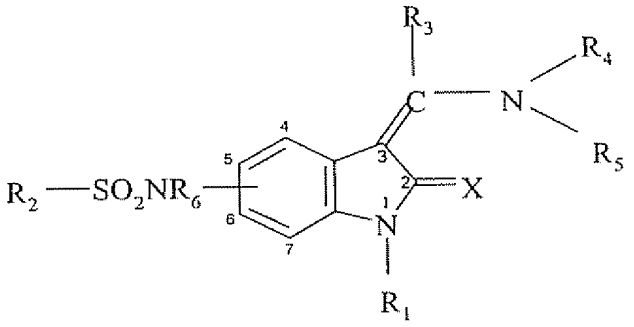
active substance	100 0 mg
polyethyleneglycol (M W 1500)	600 0 mg
polyethyleneglycol (M W 6000)	460 0 mg
polyethylenesorbitan monostearate	840.0 mg
	2,000 0 mg

Preparation:

The polyethyleneglycol is melted together with polyethylene sorbitan monostearate. At 40°C the ground active substance is homogeneously dispersed in the melt. It is cooled to 38°C and poured into slightly chilled suppository moulds

Patent Claims

1 Substituted indolinones of general formula I



(I),

the isomers, the salts thereof, particularly the physiologically acceptable salts thereof, wherein

X denotes an oxygen or sulphur atom,

R_1 denotes a hydrogen atom, a C_{1-4}-alkoxycarbonyl or C_{2-4}-alkanoyl group,

R_2 denotes a C_{1-6}-alkyl group optionally substituted by one or more halogen atoms or a phenyl group or a C_{2-6}-alkenyl group optionally substituted by a phenyl group, wherein the phenyl moiety may be substituted in each case by a fluorine, chlorine, bromine or iodine atom, by a C_{1-3}-alkyl or C_{1-3}-alkoxy group,

a phenyl group which may be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-3}-alkyl or C_{1-3}-alkoxy groups, wherein the substituents may be identical or different,

a phenyl group substituted by a trifluoromethyl, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, cyano, aminomethyl, nitro or amino group,

a C_{4-6}-alkyl, C_{3-7}-cycloalkyl, trimethylphenyl or naphthyl group,

a 5-membered heteroaromatic group optionally substituted by a C_{1-3}-alkyl group, which contains, in the heteroaromatic moiety,

an imino group optionally substituted by a C_{1-3}-alkyl group, an oxygen or sulphur atom,

an imino group optionally substituted by a C_{1-3}-alkyl group and an oxygen, sulphur or nitrogen atom,

an imino group optionally substituted by a C_{1-3}-alkyl group and two nitrogen atoms, or

an oxygen or sulphur atom and two nitrogen atoms, and to which a phenyl ring may be fused via two adjacent carbon atoms,

or denotes a 6-membered heteroaromatic group optionally substituted by a C_{1-3}-alkyl group, which contains one or two heteroatoms in the heteroaromatic moiety and to which a phenyl ring may be fused via two adjacent carbon atoms,

R_3 denotes a hydrogen atom or a C_{1-6}-alkyl group,

a phenyl group optionally substituted by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl, hydroxy, C_{1-3}-alkoxy, C_{1-3}-alkylsulphenyl, C_{1-3}-alkylsulphinyl, C_{1-3}-alkylsulphonyl, phenylsulphenyl, phenylsulphinyl, phenylsulphonyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{2-5}-alkanoylamino or N-(C_{1-3}-alkylamino)-C_{2-5}-alkanoylamino group,

R4 denotes a phenyl or naphthyl group optionally substituted by R_7, which may additionally be substituted by a chlorine or bromine atom or a nitro group, a 5-membered heteroaromatic group which contains an imino group, an oxygen or sulphur atom or an imino group, an oxygen or sulphur atom and one or two nitrogen atoms, or

a 6-membered heteroaromatic group which contains one, two or three nitrogen atoms, while the abovementioned 5- and 6-membered heteroaromatic groups may additionally be substituted by a chlorine or bromine atom or by a methyl group or wherein a phenyl ring may be fused to the abovementioned 5- and 6-membered heteroaromatic groups via 2 adjacent carbon atoms, or

R_5 and R_6 in each case independently of one another denote hydrogen atoms or C_{1-3}-alkyl groups, and

R_7 denotes a fluorine, chlorine, bromine or iodine atom or a cyano group,
a methoxy group or a C_{2-3}-alkoxy group, which may be substituted in the 2 or 3 position by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino or 5- to 7-membered cycloalkyleneimino group, while in each case an alkyl moiety in the abovementioned alkylamino and dialkylamino groups may additionally be substituted by a phenyl group,

a trifluoromethyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{2-5}-alkanoylamino, N-(C_{1-3}-alkyl)-C_{2-5}-alkanoylamino, C_{1-5}-alkylsulphonylamino, N-(C_{1-3}-alkyl)-C_{1-5}-alkylsulphonylamino, phenylsulphonylamino, N-(C_{1-3}-alkyl)-phenylsulphonylamino, aminosulphonyl, C_{1-3}-alkylaminosulphonyl or di-(C_{1-3}-alkyl)-aminosulphonyl group, while in each case an alkyl moiety in the abovementioned alkylamino and dialkylamino groups may additionally be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, 2-dimethylaminoethylaminocarbonyl or N-methyl-(2-dimethylaminoethyl)-aminocarbonyl group and in each case the alkyl moiety of the abovementioned alkanoylamino or alkysulphonylamino groups may additionally be substituted by a phenyl, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino or a 4- to 7-membered cycloalkyleneimino group,

a C_{2-4}-alkylamino group which is terminally substituted in the 2, 3- or 4 position by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, benzylamino, N-(C_{1-3}-alkyl)-benzylamino, C_{2-5}-alkanoylamino or N-(C_{1-3}-alkyl)-C_{2-5}-alkanoylamino group and wherein additionally the amino-hydrogen atom may be replaced by a C_{2-5}-alkanoyl, benzoyl, C_{1-5}-alkylsulphonyl- or phenylsulphonyl group, while the last-mentioned C_{2-5}-alkanoyl or C_{1-5}-alkylsulphonyl groups in the alkyl moiety may be substituted by a phenyl group,

a carbonyl group which is substituted by a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino, N-(C_{1-5}-alkyl)-C_{1-3}-alkylamino or C_{5-7}-cycloalkyleneimino group;

a C_{1-3}-alkyl group which may be substituted by an amino, C_{1-5}-alkylamino, C_{5-7}-cycloalkylamino or phenyl-C_{1-3}-alkylamino group which may additionally be substituted at the amino nitrogen atom in each case by a C_{1-4}-alkyl, C_{5-7}-cycloalkyl or C_{2-4}-alkenyl- or C_{1-4}-alkyl group, while

the abovementioned C_{1-4}-alkyl substituent in each case may additionally be mono-, di- or trisubstituted by a cyano, carboxy, C_{1-3}-alkoxycarbonyl, C_{2-4}-alkanoyl, pyridyl, imidazolyl, benzo[1,3]dioxol or phenyl group, while the phenyl group may be substituted by fluorine, chlorine or bromine atoms, by methyl, methoxy, trifluoromethyl, cyano or nitro groups and the substituents may be identical or different, or in the 2, 3 or 4 position by a hydroxy group,

a C_{1-3}-alkyl group which is substituted by a hydroxy, carboxy, morpholino, thiomorpholino, 1-oxo-thiomorpholino, 1,1-dioxo-thiomorpholino, piperazino, N-(C_{1-3}-alkyl)-piperazino or N-benzyl-piperazino group, by a 5- to 7-membered cycloalkenyleneimino group or by a 4- to 7-membered cycloalkyleneimino group, while the abovementioned 5- to 7-membered cycloalkyleneimino groups may be substituted by one or two C_{1-3}-alkyl groups, which may in turn be terminally substituted by amino or C_{2-4}-alkanoylamino group, or by a C_{5-7}-cycloalkyl or phenyl group and by a hydroxy group and in the abovementioned cycloalkyleneimino groups a methylene group adjacent to the nitrogen atom may be replaced by a carbonyl group,

a C_{1-3}-alkyl group which is substituted by a 5- to 7-membered cycloalkyleneimino group, while a phenyl group optionally mono- or disubstituted by fluorine, chlorine or bromine atoms or by methyl or methoxy groups, wherein the substituents may be identical or different, or an oxazolo, imidazolo, thiazolo, pyridino, pyrazino or pyrimidino group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a methyl, methoxy or amino group is fused to the abovementioned 5- to 7-membered cycloalkyleneimino groups via 2 adjacent carbon atoms, while the

abovementioned monosubstituted phenyl groups may additionally be substituted by a fluorine, chlorine or bromine atom, by a methyl, methoxy or nitro group, or

an imidazolyl or 1H-C_{1-3}-alkylimidazolyl group

2 Compound of formula I according to claim 1 wherein the sulphonylamino group of the formula R_2-SO_2NR_6- is linked to the 5-position of the indolinone group

3 Compound of formula I according to claim 1 or 2 wherein

R_3 denotes a phenyl group optionally substituted by a fluorine, chlorine or bromine atom, by a C_{1-3}-alkyl, hydroxy, C_{1-3}-alkoxy, C_{1-3}-alkylsulphenyl, C_{1-3}-alkylsulphinyl, C_{1-3}-alkylsulphonyl, phenylsulphenyl, phenylsulphinyl, phenylsulphonyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{2-5}-alkanoylamino or N-(C_{1-3}-alkylamino)-C_{2-5}-alkanoylamino group

4 Compound of formula I according to one of claims 1 to 3 wherein

R_2 denotes a C_{1-3}-alkyl group optionally substituted by one or more halogen atoms or a phenyl group or a C_{2-4}-alkenyl group optionally substituted by a phenyl group, wherein the phenyl moiety in each case may be substituted by a fluorine, chlorine, bromine or iodine atom or by a C_{1-3}-alkyl or C_{1-3}-alkoxy group

5 Compound of formula I according to one of claims 1 to 4 wherein

X denotes an oxygen atom,

R_1 denotes a hydrogen atom,

R_2 denotes a C_{1-3}-alkyl group optionally substituted by one or more fluorine atoms or a phenyl group or a C_{2-4}-alkenyl group optionally substituted by a phenyl group;

a phenyl group which may be mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-3}-alkyl or C_{1-3}-alkoxy groups, wherein the substituents may be identical or different,

a phenyl group substituted by a trifluoromethyl, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, cyano, aminomethyl, nitro or amino group,

a C_{4-6}-alkyl, C_{3-7}-cycloalkyl, trimethylphenyl or naphthyl group, or

a pyridinyl, quinolyl, isoquinolyl, oxazolyl, isoxazolyl, imidazolyl or 1-(C_{1-3}-alkyl)-imidazolyl group optionally substituted by a C_{1-3}-alkyl group,

R_3 denotes a hydrogen atom or a C_{1-4}-alkyl group, or

a phenyl group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a C_{1-3}-alkyl, C_{1-3}-alkoxy, nitro or amino group,

R_4 denotes a phenyl group optionally substituted by R_7,

R_5 and R_6 in each case denote a hydrogen atom, and

R_7 denotes a fluorine, chlorine, bromine or iodine atom,

a methoxy, nitro, cyano, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylaminocarbonyl, N-(phenyl-C_{1-3}-alkyl)-C_{1-3}-alkylaminocarbonyl or 5- to 7-membered cycloalkyleneiminocarbonyl group,

a C_{1-3}-alkyl group which is substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylaminocarbonyl, N-(phenyl-C_{1-3}-alkyl)-C_{1-3}-alkylaminocarbonyl, 5- to 7-membered cycloalkyleneiminocarbonyl, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-

amino, phenyl-C_{1-3}-alkylamino, N-(phenyl-C_{1-3}-alkyl)-C_{1-3}-alkylamino or 5- to 7-membered cycloalkyleneimino group,

while the abovementioned 5- to 7-membered cycloalkyleneimino moieties may be substituted by one or two C_{1-3}-alkyl groups and at the same time in the abovementioned 5- to 7-membered cycloalkyleneimino moieties, a methylene group in the 2 position may be replaced by a carbonyl group or in the abovementioned 6- and 7-membered cycloalkyleneimino moieties a methylene group in the 4 position may be replaced by an oxygen atom, by an imino, N-(C_{1-3}-alkyl)-imino, N-(phenyl-C_{1-3}-alkyl)-imino or N-(C_{1-5}-alkoxycarbonyl)-imino group,

an amino, C_{1-3}-alkylamino, phenyl-C_{1-3}-alkylamino, C_{1-5}-alkanoylamino, phenyl-C_{1-4}-alkanoylamino, C_{1-5}-alkoxycarbonylamino, phenyl-C_{1-3}-alkoxycarbonylamino, C_{1-5}-alkylsulphonylamino, phenyl-C_{1-3}-alkylsulphonylamino- or phenylsulphonylamino group, wherein the hydrogen atom of the amino group may be replaced by a C_{1-3}-alkyl group, while the C_{1-3}-alkyl moiety may be substituted by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylaminocarbonyl, N-(phenyl-C_{1-3}-alkyl)-C_{1-3}-alkylaminocarbonyl or C_{4-6}-cycoalkylenimnocarbonyl group or from position 2 by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkylamino, N-(phenyl-C_{1-3}-alkyl)-C_{1-3}-alkylamino, C_{2-5}-alkanoylamino, N-(C_{1-3}-alkyl)-C_{2-5}-alkanoylamino, C_{1-5}-alkoxycarbonylamino or N-(C_{1-5}-alkoxycarbonyl)-C_{1-3}-alkylamino group.

6. Compound of formula I according to one of claims 1 to 5 wherein

R_2 denotes a C_{1-3}-alkyl group optionally substituted by a phenyl group, a C_{1-3}-perfluoroalkyl group or a phenylvinyl group,

a phenyl group which may be substituted by a fluorine, chlorine, bromine or iodine atom, by a C_{1-3}-alkyl, C_{1-3}-alkoxy, nitro, amino, cyano, cyanomethyl or aminomethyl group,

a C_{4-6}-alkyl, C_{3-7}-cycloalkyl, trimethylphenyl or naphthyl group, or

a pyridinyl, quinolyl, isoquinolyl, oxazolyl, isoxazolyl, imidazolyl or 1-(C_{1-3}-alkyl)-imidazolyl group optionally substituted by a C_{1-3}-alkyl group,

R_3 denotes a phenyl group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a C_{1-3}-alkyl, C_{1-3}-alkoxy, nitro or amino group,

R_4 denotes a phenyl group which may be substituted by R_7 and additionally by a chlorine atom or a nitro group, while

R_7 denotes a fluorine, chlorine, bromine or iodine atom,

a methoxy, nitro, cyano, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, benzylaminocarbonyl, N-benzyl-methylaminocarbonyl, pyrrolidinocarbonyl or piperidinocarbonyl group,

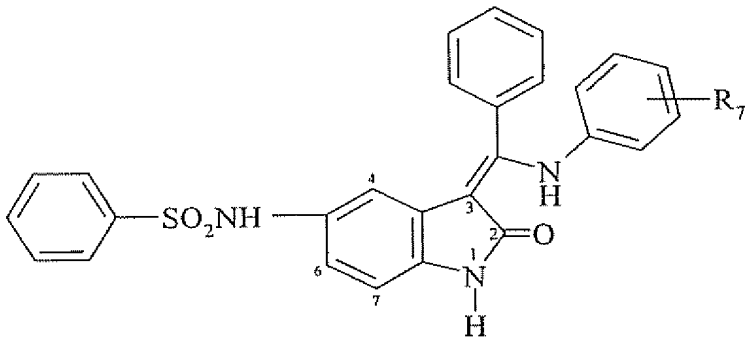
a methyl or ethyl group which may be substituted by a carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, benzylaminocarbonyl, N-benzyl-methylaminocarbonyl, pyrrolidinocarbonyl, piperidinocarbonyl, amino, methylamino, dimethylamino, benzylamino, N-benzyl-methylamino, C_{2-4}-alkanoylamino, N-methyl-C_{2-4}-alkanoylamino, tert butyloxycarbonylamino, N-methyl-tert butyloxycarbonylamino, pyrrolidino, piperidino, dimethylpiperidino, 2-oxo-piperidino, piperazino, 4-methyl-piperazino, 4-benzyl-piperazino, 4-tert butoxycarbonyl-piperazino or morpholino group, or

an amino, methylamino, ethylamino, C_{1-3}-alkanoylamino, phenylacetylamino, tert butoxycarbonylamino, C_{1-4}-alkylsulphonylamino, phenyl-methylsulphonylamino or phenylsulphonylamino group, wherein the hydrogen atom of the amino group may be replaced by a methyl or ethyl group, while the methyl or ethyl moiety in each case may be substituted by a carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl or dimethylaminocarbonyl group or the ethyl moiety may also

be substituted from position 2 by an amino, methylamino, dimethylamino, benzylalkylamino, N-benzyl-methylamino, C_{2-3}-alkanoylamino, N-methyl-C_{2-3}-alkanoylamino, tert butyloxycarbonylamino or N-methyl-tert butyloxycarbonylamino group

7 Compound of formula I according to one of claims 1 to 6 wherein R_4 denotes a phenyl group substituted in the 4 position by R_7

8 Compound of formula IA



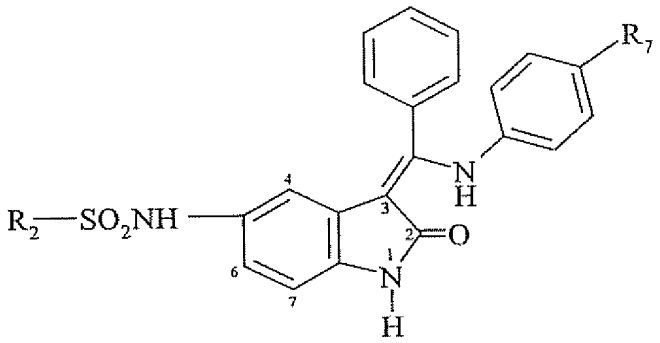
(IA),

wherein R_7 has the meaning given in claims 1 to 7

9 Compound of formula IA according to claim 8 wherein R_7 is selected from among: hydrogen, (2,6-dimethylpiperidino)-methyl, (N-ethylsulphonyl)-N-(2-dimethylaminoethyl)-aminocarbonylmethyl)-amino, N-ethylsulphonyl-N-(N-(2-dimethylaminoethyl)-N-methyl-amino-carbonylmethyl)-amino, 2-oxopiperidinomethyl, 4-benzyl-piperazino-methyl, 4-methylpiperazino-methyl, 4-tert butoxycarbonyl-piperazinomethyl, acetylamino, acetylaminomethyl, amino, aminomethyl, benzylaminocarbonyl, benzylaminocarbonyl-methyl, carboxy, carboxymethyl, chlorine, cyano, dimethylaminocarbonyl-methylamino, dimethylaminoethyl, dimethylaminomethyl, ethoxycarbonylmethyl, ethylsulphonylamino, formylamino, methoxycarbonyl, methylsulphonylamino, morpholinomethyl, N-(2-(N-acetyl-N-methyl-amino)-ethyl)-ethylsulphonylamino, N-(2-(N-acetyl-N-methyl-amino)-ethyl)-methylsulphonylamino, N-(2-(N-acetyl-N-methyl-amino)-ethyl)-propionylamino, N-(2-(N-acetyl-N-methyl-amino)-ethylamino, N-(2-(N-benzyl-N-methyl-amino)-ethyl)-propionyl-amino, N-(2-acetylamino-ethyl)-N-acetyl-amino, N-(2-acetylamino-ethyl)-N-ethylsulphonyl-amino, N-(2-acetylamino-ethyl)-N-methylsulphonyl-amino, N-(2-acetylamino-ethyl)-N-

propionyl-amino, N-(2-aminoethyl)-N-methylsulphonyl-amino, N-(2-dimethylamino-ethyl)-N-acetyl-amino, N-(2-dimethylamino-ethyl)-N-butylsulphonyl-amino, N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino, N-(2-dimethylamino-ethyl)-N-phenylsulphonyl-amino, N-(2-dimethylaminoethyl)-N-propylsulphonyl-amino, N-(2-methylamino-ethyl)-acetylamino, N-(2-methylamino-ethyl)-N-methylsulphonyl-amino, N-(2-methylamino-ethyl)-propionylamino, N-(2-propionylamino-ethyl)-N-propionyl-amino, N-(aminocarbonyl-methyl)-N-methylsulphonyl-amino, N-(dimethylamino-carbonylmethyl)-N-(methylsulphonyl-amino, N-(dimethylaminoethyl)-N-methylsulphonyl-amino, N-(methylaminocarbonyl-methyl)-N-methylsulphonyl-amino, N-(piperidinomethyl-carbonyl)-N-methyl-amino, N-acetyl-N-(2-(N-benzyl-N-methyl-amino)-ethylamino, N-acetyl-N-(2-benzyl-oxycarbonylamino-ethyl)-amino, N-carboxylmethyl-N-methylsulphonyl-amino, N-ethylsulphonyl-N-hydroxycarbonylmethyl-amino, N-methyl-N-acetyl-amino, N-methyl-N-ethylsulphonyl-amino, N-methyl-N-formyl-amino, N-methyl-N-methylsulphonyl-amino, N-methyl-N-propionyl-amino, piperazinomethyl, propionylamino, pyrrolidin-1-yl-methyl and tert butoxycarbonylamino

Compound of formula IB



(IB),

wherein R_2 and R_7 have the meanings given in claims 1 to 7

11. Compound of formula IB according to claim 10 wherein R_7 has one of the meanings given in claim 7 and R_2 is selected from among:
1-methyl-1H-imidazol-4-yl, 2-aminophenyl, 2-chlorophenyl, 2-cyanophenyl, 2-nitrophenyl, 2-phenylethene, 3-aminomethylphenyl, 3-aminophenyl, 3-chlorophenyl, 3-cyanophenyl, 3-methoxyphenyl, 3-methylphenyl, 3-nitrophenyl, 4-aminophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-methylphenyl, 4-nitrophenyl, benzyl, quinolin-8-yl, cyclopropyl, ethyl,

isopropyl, methyl, naphthalin-1-yl, naphthalin-2-yl, propyl, pyrid-2-yl, pyrid-3-yl, 3,5-dimethyl-isoxazol-4-yl and 2,4,6-trimethylphenyl

12 A compound of formula I selected from among:

(Z)-3-{1-[4-(N-(2-aminoethyl)-N-methylsulphonyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(N-(2-dimethylaminoethyl)-N-phenylsulphonyl-amino)-phenylamino)-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(4-methylpiperazinomethyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(N-methyl-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone

(Z)-3-(1-phenylamino-1-phenyl-methylidene)-5-phenylsulphonylamino-2-indolinone

(Z)-3-[1-(4-chlorophenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(N-(2-propionylamino-ethyl)-N-propionyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone

(Z)-3-[1-(4-dimethylaminomethyl-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indole

(Z)-3-[1-(4-(N-methyl-N-methylsulphonyl-amino)-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone

(Z)-3-[1-(4-(N-methyl-N-piperidinomethylcarbonyl-amino)-phenylamino)-1-phenyl-methylidene]-5-phenylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-benzylsulphonylamino-2-indolinone

(Z)-3-{1-[4-((2,6-dimethylpiperidino)-methyl)-phenylamino]-1-phenyl-methylidene}-5-(3-nitrophenylsulphonylamino)-2-indolinone

(Z)-3-{1-[4-dimethylaminomethyl-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(N-benzyl-N-methyl-aminomethyl)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(2-dimethylamino-ethyl)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-indolinone

(Z)-3-{1-[4-(pyrrolidin-1-ylcarbonyl)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylsulphonylamino)-2-indolinone

(Z)-3-[1-(4-piperidinomethyl-phenylamino)-1-phenyl-methylidene]-5-methylsulphonylamino-2-indolinone (Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-isopropylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(naphthalin-1-ylsulphonylamino)-2-indolinone

(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(3-nitrophenylsulphonylamino)-2-indolinone

(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(3,5-dimethylisoxazol-4-ylsulphonylamino)-2-indolinone

(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-cyclopropylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(piperidinomethyl)-phenylamino]-1-phenyl-methylidene}-5-(pyridin-3-ylphenylsulphonylamino)-2-indolinone

(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-cyclopropylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-propylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-ethylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(pyrrolidin-1-ylmethyl)-phenylamino]-1-phenyl-methylidene}-5-methylsulphonylamino-2-indolinone

(Z)-3-{1-[4-(benzylaminocarbonyl)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone

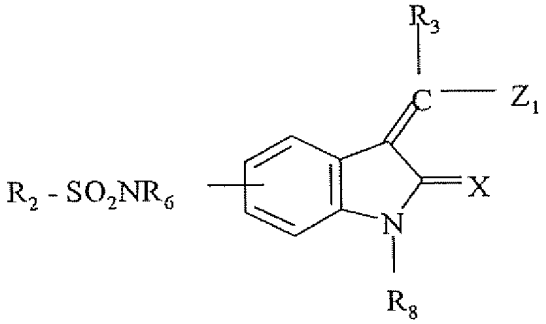
(Z)-3-{1-[4-(N-dimethylaminocarbonylmethyl-N-acetyl-amino)-phenylamino]-1-phenyl-methylidene}-5-phenylsulphonylamino-2-indolinone

(Z)-3-[1-(4-piperidinomethyl-phenylamino)-1-phenyl-methylidene]-5-(4-aminophenylsulphonylamino)-2-indolinone

(Z)-3-{1-[4-(N-(2-dimethylamino-ethyl)-N-methylsulphonyl-amino)-phenylamino)-1-phenyl-methylidene}-5-(N-methyl-N-phenylsulphonyl-amino)-2-indolinone

13. Process for preparing a compound of formulae I, IA or IB according to one of claims 1 to 11, characterised in that

(a) a compound of general formula



(II),

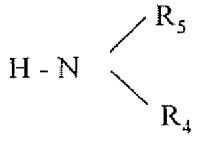
wherein

X, R_2, R_3 and R_6 are as hereinbefore defined and

R_8 has one of the meanings given for R_1 or denotes a protecting group for the nitrogen atom of the lactam group, while R_8 may also denote a bond to a solid phase optionally formed via a spacer, and

Z_1 denotes a halogen atom, a hydroxy, alkoxy or aralkoxy group, e g a chlorine or bromine atom, a methoxy, ethoxy or benzyloxy group,

is reacted with an amine of general formula III



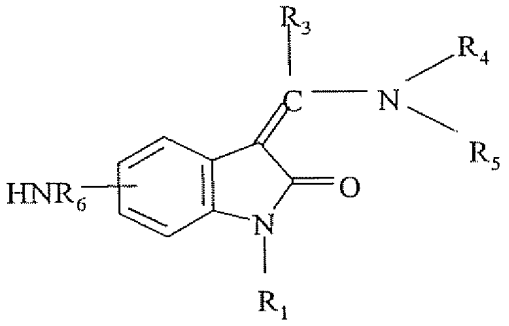
(III),

wherein

R_4 and R_5 are as hereinbefore defined,

and if necessary any protecting group used for the nitrogen atom of the lactam group is cleaved or is cleaved from a solid phase; or

(b) a compound of general formula



(IV),

wherein

R_1 and R_3 to R_6 are as hereinbefore defined, is reacted with a compound of general formula

$$R_2 - SO_2 - OH \quad (V),$$

wherein

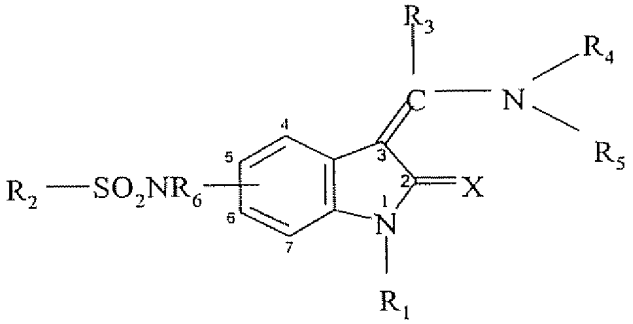
R_2 is as hereinbefore defined, or with the reactive derivatives thereof.

14. Pharmaceutical preparation containing a compound according to one of claims 1 to 11 and pharmaceutically acceptable carriers and/or excipients

15. Use of a compound according to one of claims 1 to 11 for preparing a medicament for the treatment and prevention of diseases characterised by excessive or abnormal cell proliferation.

Abstract

The invention relates to substituted indolinones of general formula I



(I),

the isomers, the salts thereof, particularly the physiologically acceptable salts thereof, wherein R_1, R_2, R_3, R_4, R_5, R_6 and X have the meanings given in claim 1, as well as processes for preparing them and their use. The new compounds are valuable inhibitors of cell proliferation, particularly of tumour cells, and inhibitors of protein kinases